

Pollution in its Place

NATIONS are now accustomed to create committees for the study of pollution with all the zeal with which, in past decades, they have created national airlines, national broadcasting networks and the like, but Britain has been lucky in the most prestigious adventure of this kind—the Standing Royal Commission on Environmental Pollution with Sir Eric Ashby as chairman (see page 586). Although the commission's first report, now published, is more a prospectus for future work than a recipe for solving present problems, it has defined a sensible framework within which the analysis of environmental problems can be conducted in a levelheaded fashion. If only the document is widely read, the result could well be a better concentration of public and political interest on issues deserving of public attention. The difficulty is that the commission's advice, like that of all other royal commissions, can be religiously ignored by everybody concerned, even the government departments that helped to set it up.

The sobriety of the commission's view of the problem with which it has been saddled is well exemplified by what it has to say about the criteria on which decisions about the abatement of environmental nuisances should be based. The starting point for the discussion is a careful statement of the problem. The issue, the commission implies, is not so much how to abate pollution as of deciding how much to spend on abating pollution. Theoretical models are easy to construct, as any elementary textbook in economics will show. The commission says that the criterion for how much to spend is that pollution should be reduced to the point at which the costs are matched by the benefits. Presumably its intention is that in an ideally calculable world, the marginal costs and benefits should be equal. The immediate difficulty is that nobody has sure ways of calculating even the costs of reducing some particular forms of pollution to some predetermined level. Quantifying the benefits is, as the commission points out, necessarily a more chancy business, involving attempts to put a figure on the value of particular social assets. This is why the committee says—and everybody will applaud—that serious attempts should be made to define the economic quantities involved. But what will happen if nobody has the wit to provide an answer? One of the few parts of this first report at which the commission abandoned argument for arm-waving is that in which it draws an analogy between the way countries such as Britain have spent large sums on education without being able to put a figure to the benefits, and says that pollution and its abatement must similarly be dependent on value judgments. And if slavery has been abolished without the economic cost being held to be an obstacle to reform, is it not now sensible that society should “willingly incur expenditure on the protection of its own natural environment”?

Rhetorically, the question is unanswerable. In the years ahead, however, it is important that society should find ways of using in cost benefit equations factors which represent social benefits which are not easily quantified. To begin with, it is often the case that apparently imponder-

able benefits can be partially defined by means of upper or lower limits. In Britain, for example, it is by now well established that the death rate from bronchitis in north-west England is far greater than that south of the Thames and, even though climate and age distribution in the population may be concerned, so too is almost certain to be atmospheric pollution in the larger cities. After all, it is only a decade since old people in their hundreds were killed off in northern cities when sulphur dioxide and other noisome products were trapped beneath inversion layers. The Clean Air Acts notwithstanding, it is not improbable that air pollution as a cause of verifiable death continues in many parts of Britain. Here, then, is one means of providing a sombre lower limit to the number to be entered in the cost benefit equation. The fact that less tangible factors such as the possibility that there may be a link between air pollution of some kinds and lung cancer, for example, or the likelihood that clean air may enable people to be more cheerful cannot easily be cast in numerical form should be regarded not as a proof that the cost benefit equation is insoluble, but that there is a need for a better understanding of the factors not already quantifiable. The commission's use of the analogy of slavery and its abolition is in any case not all that convincing a proof that there must be circumstances in which important questions must be decided on stark ethical principles: apartheid in South Africa is an offence against decent values but also in an advancing society an economic handicap as well.

On the issue of which nuisances to deal with first, the commission also spells out the helpful principle that the management of the environment must be a deliberate process, with no crash programmes to distract attention from long-term goals. This is one of the most serious pitfalls in the planning of the environment. The temptation is to tackle first the problems that are easiest to solve. Where governments are concerned, it is also tempting first of all to deal with apparent nuisances which are cheap to abolish. This is much the spirit in which governments have sought to rid the environment of DDT and other persistent pesticides by imposing restrictions on manufacturers before anybody has had a chance to ensure that such a course will not entail an unwarrantable cost in crops or even lives destroyed by pests. By comparison, governments, even enthusiastic governments such as that in Washington, are comparatively slow to hand out public money for the abatement of public nuisances such as the practice in the United States of discharging large quantities of untreated sewage into rivers. If the Ashby commission's precept is to be taken seriously, the movement for a better environment will not merely be costed more precisely than in the past but will be given some sense of strategy to replace what has recently been a frenetic and over-zealous anxiety to do something that shows and which is quick. The commission does well to point out that the almost spectacular improvement of air pollution in Britain, a 50 per cent decrease of smoke pollution in a decade, has cost many millions of pounds spread over many years. This is not a field for fickle enthusiasts.



If the Ashby commission has left the economics of pollution for study by some other branch of government, it has also unfortunately skated over some of the legal issues to be decided. In the past several years, there has been a tendency to assume that only governments can act decisively in the abatement of public nuisances and, indeed, the spectacular developments of the recent past have all been represented by government decisions. But unfortunately, however, governments cannot always be relied upon to act decisively or even diligently, which implies that there is a need somehow to improve the institutions regulating the conditions of rivers, coasts and even the atmosphere. The ideal is that there should be self-correcting legal instruments or institutional arrangements which can help to make sure that those who use the environment in various ways are much more aware than at present of the potential cost of doing so. Where the pollution of rivers is concerned, for example, it would be only sensible if the statutory authorities called river boards which at present control some of the uses made of rivers were also given authority for the disposal of sewage in the corresponding catchment areas. This, as it happens, is one of the commission's specific recommendations in its first report and here, as luck will have it, there is a chance that the British government will do something effective. The general principle should be that opposing interests should as often as possible be fitted into the same framework of regulation and control.

However vigorous the war against pollution, however, nobody can be sure that the outcome will be a marked

improvement in the quality of life as it is called. The trouble, of course, is that no amount of air cleansing equipment can make life in a badly planned city delightful. This is another of the general points made by the Ashby commission and one that should be taken seriously. If countries such as Britain are now determined to spend considerable sums on measures for the more effective control of pollution, they should also ask themselves whether the same result might not be achieved more simply and even more cheaply by more imaginative planning of cities and the countryside. Aircraft noise is the illustration that cries out for attention. Is it better that there should be research and development leading to less noisy but less efficient aircraft engines, or that there should be a sensible policy for the siting of airfields at places where the noise the aircraft make is immaterial? Similarly, in cities, a part at least of the traffic problem could be made to disappear if cities were planned in such a way that the need for physical movement was reduced or, alternatively, if orderly public transport were more attractive. This is a powerful reason why it will be a great misfortune if current concern about the environment, well intentioned and potentially beneficent as it is, turns out to be restricted simply to a campaign against pollution. Moreover, it is important to acknowledge that getting rid of pollution of any kind, like the building of more decently organized cities, is bound to be an expensive social investment. On the face of things, it looks very much as if the Ashby commission will turn out to be a powerful spur in this direction.

Teaching without Research

THE changing pattern of financial support for scientific research at universities was bound to have profound and lasting effects on the character of academic life and, in due course, on the character of university departments. The report of the Chemistry Committee of the Science Research Council (see page 587) is the latest sign of the way the wind is blowing. To begin with, the committee calculates that if there were to be a substantial increase in the annual output of PhD graduates there would be a problem in finding jobs for everybody. Luckily, it looks as if the annual output of PhD graduates will in fact be stabilized at less than 900, of whom 200 a year will find their way into teaching posts at British universities. The committee also draws attention to the need for some alternative method of allotting studentships to university departments so as to allow for the way in which a steadily growing number of university departments are anxious to take on the training of graduates and the academic research programmes which traditionally accompany this process. The solution, the committee suggests—and it is plainly flying a kite and not laying down policy—may be a more selective way of choosing the departments to which studentships will be allocated. Because in Britain the Science Research Council is a predominant source of stipends for potential PhD graduates, a process any more selective than at present used would be certain to have a powerful influence on the pattern of graduate training at the universities. What the committee is looking for is a formula for making sure that some would-be graduate schools will have no students to teach.

For the departments concerned, the consequences could be far-reaching, if only because the regular subvention of universities by the University Grants Committee is calculated after taking account of staff-student ratios which are more generous when the students are already graduates. A department denied studentships would quickly become a department in which research would have to be squeezed into a much more crowded teaching programme than at present and would be without the benefit of the interaction between teachers and graduate students. Will this not imply that in the comparatively near future, there will be a situation in which some university departments will be demonstrably different from others, more pre-occupied with teaching and less with research? On the face of things, this would seem to be inevitable in the present situation in which the number of universities, or of university departments in particular disciplines, is too great for the amount of money available for research, but too little to satisfy the legitimate demands for undergraduate instruction. Moreover, it is important that even if the amount of money available for research were for practical purposes unlimited, the preservation of the genteel convention that all university departments can be graduate schools if they choose would create horrendous anomalies. In the sciences as a whole, roughly a third of all successful PhD candidates at present find their way into university teaching and the simple truth is that with present ratios of staff members to graduate students, a PhD graduate will more than replace himself during his career. In other words, either the amount of graduate training

done by the university departments must be reduced or some ways must be conjured up for employing PhD graduates outside the universities—an unlikely prospect in present circumstances. The result seems unavoidable, and applies to departments other than chemistry departments—that in the future there is bound to be a modification of the old principle that all university teachers can be active research workers unless they decide otherwise. For one thing, there is not enough money. For another, the traditional assumption that research and the training of graduates must go hand in hand can only be implemented by training people for jobs that do not exist. It goes without saying that these tendencies will, if anything, be strengthened by the growing competence of the polytechnics in graduate training.

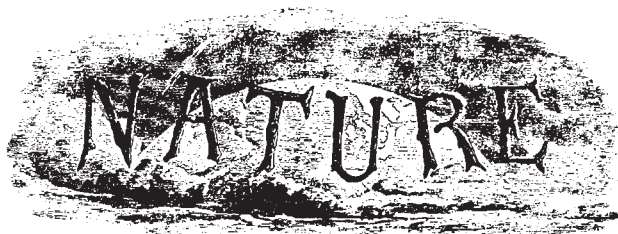
How should the universities respond? The first thing to say is that there is no special reason why universities should hang their heads in shame if some of them are forced by circumstances to concentrate on teaching. This, after all, is why they exist. In Britain, however, universities are unnecessarily fragmented by the tendency of the larger university departments towards fission. Every chemistry department, after all, is now at least a troika of inorganic, physical and organic chemistry. Biochemistry is usually something quite different. The result is that such research effort as there is must be scattered even more widely than is strictly necessary among a multiplicity of university departments and sub-departments. It is no wonder that many of these institutions are hard pressed to devise viable research programmes for themselves. Often, everything will rest on the shoulders of one energetic man with a clear idea of what he wants to do—and, by the same test, everything will collapse when he in his turn is snatched away to a more powerful appointment somewhere else. So is it not necessary, in the year ahead, that as a part of their adjustment to changing circumstances, university departments which have been traditionally split apart should be welded together in such a way that those academics whose energies will be principally concentrated on teaching should be enabled to rub shoulders and exchange ideas with people who are more actively engaged on research? Is it not also necessary to acknowledge that some university departments consecrated to subjects such as biochemistry and busily teaching undergraduates should be persuaded that their future also lies within a wider and more flexible framework? Biochemistry, after all, is hardly the kind of diet to be fed to undergraduates undiluted. In short, there is a need that universities in self-defence should do whatever they can to reorganize departments in such a way as to make them bigger, better coordinated and more capable of providing undergraduates with a variety of courses. The alternative is a more open and more immediate recognition that some university departments must be and will be treated less well than others in the same field.

There is also a need for some change in what is considered to be a proper activity for academics. In the years since the war, the convention has grown up that in the natural sciences, scholarship is represented principally by experimental research or some other activity absorbing most of every working day. Perhaps the time has come to ask whether this convention is essential. May there not even be advantages in a situation in which, as in the old days before the Second World War, research tended to occupy the months in the summer when the under-

graduates were away? Then, at least, this scholarly activity would be something to look forward to. To be sure, in circumstances like these, it would be necessary to discard the convention that academic promotion is determined chiefly by production in academic research.

It goes without saying that the impending change, gradual though it will be, is certain to create tensions between the universities in which research will seem increasingly privileged or even a luxury and the research institutes elsewhere in which research is a full-time occupation. This is yet another reason for hoping that the inquiry into the pattern of British research now under way will look squarely in the face the problem of the intramural research carried out by the research councils, especially the Agricultural Research Council, the Medical Research Council and the Natural Environment Research Council. Nobody would expect there to be rapid changes in present arrangements and it is also important to devise some means of making sure that there remain ways in which some kinds of research of high quality can be carried on without the encumbrance of undergraduate teaching. In other words, there is a case for a much closer association between research institutes and universities—which is not in any sense to suggest that there are no close relationships at present. What this implies is that the coming pressure on resources for research will bring about a change not merely in the amount of research carried out in universities but in the quality of academic life as well. As things stand, the universities have it within their power to ensure that the qualitative change is not a deterioration.

100 Years Ago



Sanitary Tests

DR. LANKESTER recently pointed out in *NATURE* that the existence and spread of fever were mainly owing to popular ignorance and the neglect of physiological laws. Since the article referred to was written, a greater plague has followed the fever then prevailing; and we are now told that Ireland is much better off than England—vaccination being there almost universal.

This state of things seems to me but a symptom of a more deeply-rooted evil, viz., the general neglect of physiological and sanitary science among the *higher* orders as well as the lower.

In how many large schools are the laws affecting the human body and the relation of man's frame to the destructive and constructive elements which surround us systematically taught? Are there any?

We talk of the gross ignorance and filthy habits of the poor; but both their ignorance and their filthiness are often a part of the very conditions of their existence. Have *we* been faithful stewards in this great matter?

Allow me to draw attention to the fact that, though Government has greatly facilitated and cheapened the acquisition of other branches of science, hygiene seems entirely omitted from the programme. But knowledge must descend from the higher to the lower levels. Ought not the heads of all public schools to undergo a compulsory examination in this subject? I could adduce instances where the greatest mischief has resulted from ignorance in such high quarters.

Aigburth, Liverpool, Feb. 25

SAMUEL BARBER

From *Nature*, 3, 347, March 2, 1871.

OLD WORLD

Royal Commission Provides Framework for Study

ANOTHER report on pollution has been placed on the already overloaded desk of Mr Peter Walker, the Secretary of State for the Environment. Although the report has few concrete recommendations to make, Mr Walker would do well to study its contents very carefully. It is the first offering from the Royal Commission on pollution (HMSO, 45p), set up last year under the chairmanship of Sir Eric Ashby, and it comes up with the uncontroversial conclusion that although there has been considerable improvement in some aspects of Britain's environment, there is little room for complacency. But the chief value of the report lies in its analysis of the problems caused by pollution and in its review of the present state of Britain's environment.

The report in many ways prepares the ground for further investigation by the commission, and to this end there is an analysis of the pollution problem in terms of the costs and benefits of its abatement. Much of the analysis is old hat—the commission points out, for example, that one of the chief reasons for pollution is that the costs which it involves are not usually borne by the polluter, and there is thus insufficient incentive for pollution control. But the point that there is need for an economic framework for a full cost/benefit analysis of pollution control is made by the commission with considerable conviction. It also takes pains to point out that "the social benefits of cleaner air and water, less noise and a more pleasant landscape, have to be put into perspective with other claims on resources, such as housing, health and education".

As far as the present state of the environment is concerned, the commission has a few comforting things to say about air pollution, especially the effects of the Clean Air Act in the south of England, but it is rather more gloomy about other forms of pollution. As a result of smoke control, the winter sunshine in London has increased by 50 per cent since 1950, and in spite of an increase of 17 per cent in gross energy consumption, the emission of smoke and sulphur dioxide into the atmosphere has decreased dramatically (see Fig. 1). But conditions in some of the towns in the north of England are much less pleasant, and there, the commission says, "there is urgent need for more vigorous application of the Clean Air Act". Pollution from road vehicles is also a cause for concern, chiefly because there is insufficient knowledge about the effects of long term exposure to

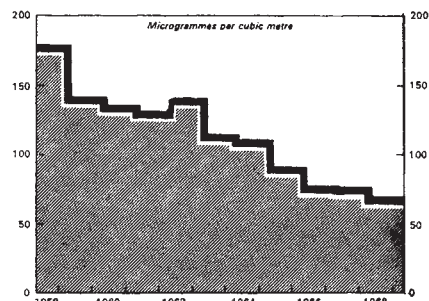


Fig. 1 Average smoke concentration near ground level in the UK, 1958-1968.

various components of exhaust fumes, and the commission warns that "it would be dangerously complacent to ignore" the projected increase in the volume of road traffic in Britain.

Turning to pollution of the land, Sir Eric Ashby's commission casts a glance at the United States, finds that the average amount of domestic refuse produced per person each day is nearly twice that in Britain and warns that Britain is likely to face a mounting refuse disposal problem. Already, 14 million tons are dumped on areas of unused land, and the only solution the commission has to offer is that salvage and recycling techniques must be improved. As for pesticides and fertilizers, the drive for less persistent fertilizers should be speeded up, and "valuable manure from intensive farming is being wasted", and consequently there is a growing risk of soil deterioration.

But it is in the area of marine and freshwater pollution that the commission sees most cause for concern. Although 73 per cent of Britain's rivers are classified as unpolluted, 12 per cent are either "grossly polluted" or "urgently needing attention". Pollution from phosphate fertilizers, which run off the land and lead to outbursts of aquatic plants in rivers and lakes, is not yet a grave problem but it is one which cannot be glossed over, the commission suggests, and an even higher standard of effluent purity must be achieved if the demand for domestic water is to be met. While there is cause for concern about river pollution, however, there is even more to worry about in the sea. Along the east and south coasts of England alone, for example, 5 million cubic metres of domestic waste, 3 million cubic metres of industrial waste and 7 million cubic metres of power station cooling water are dumped into the sea every day, and the commission says that "the estuaries and inshore seas are increasingly treated as an open drain and dump-

ing ground". Surprisingly, there is no evidence of widespread damage to marine life in British waters, but there is an obvious need for more research on the effects of pollution on the life of shallow seas. The situation is so serious in the eyes of the commission that it has decided to make pollution of tidal waters, estuaries and seas around Britain's coasts its chief topic of study this year.

Disposal of radioactive waste also came under the commission's scrutiny, and no immediate cause for disquiet was found. There is, however, a need to bear in mind the problems that are going to accrue from increased use of nuclear energy, and the commission suggests that, although arrangements for the disposal of radioactive material should lie in the province of international control, the problem needs foresight.

The commission also has a few things to say about some of the popular horror stories about global effects of pollutants. The so-called greenhouse effect, for example, in which the increasing amount of carbon dioxide in the atmosphere (see Fig. 2), acting as a type of window, lets

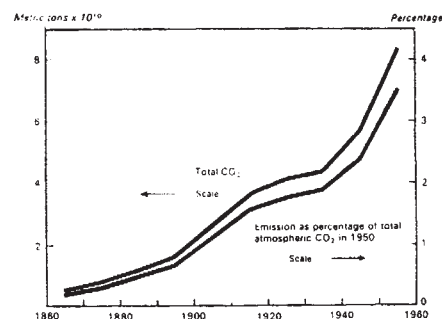


Fig. 2 Carbon dioxide from the combustion of fuels in the world, 1860-1959.

visible radiation pass through but filters out some of the long wave radiation from the Earth, has often been singled out by popular writers for dishonourable mention. The theory is that the heating up of the atmosphere which would result from this process would melt the polar ice caps, and wreak untold damage on low-lying coastal areas, but the commission says that the available evidence is not strong enough to support such a theory. More research needs to be carried out on the exchange of carbon between the oceans, plants and the atmosphere before such a theory can be proved or discredited. Nevertheless, the evidence available so far points to the possibility of an increase in

atmospheric temperature of only 0.1 to 0.2° C, and this is unlikely to be significant.

The commission comes to similar conclusions about the effects of water vapour and trace amounts of pollutants in the stratosphere—a topic which has caused considerable speculation, especially from opponents of the supersonic transporter. There is therefore “no cause for alarm” about the global effects of pollution, but the commission recommends “the extension of international monitoring of the atmosphere and the maintenance and extension of fundamental research on an international basis on the natural chemical and physical processes, both within the atmosphere and between the atmosphere and the surface of the planet”.

CERN

Green Light for 300 GeV

AFTER nearly four years of indecision and changing of plans, the CERN council has at last given the official go-ahead for the 300 GeV proton synchrotron to be built at Geneva. Ironically, the indecision and early disputes about the possible site for the accelerator have produced a relatively cheap and very flexible proposal which arose last year like a phoenix from the ashes of earlier plans. When the CERN council met last week to carry on the meeting that was adjourned last December, ten out of the twelve member states pledged their support for the plans and only two delegations—those from Greece and Denmark—had to declare their governments’ unwillingness to take part. This means that the cost of the project—estimated to be about £90 million over a period of eight years—will be divided chiefly between West Germany who will contribute 24 per cent, Britain (22.5 per cent), France (20.5 per cent) and Italy (13.3 per cent).

The council meeting was adjourned last December when it became evident that the governments of some of the smaller countries needed more time in which to make up their minds about the proposals. But agreement was also prevented because the British delegation, led by Sir Brian Flowers, was hamstrung by the condition imposed by the government that British support would only be forthcoming if the council decision were unanimous. Happily, this condition was relaxed and the British delegation was not placed in the unenviable position of watching the whole project paralysed by the abstention of Denmark and Greece.

The Greek delegation said that although it believes that the 300 GeV project is very worthwhile, the Greek government has no money to spend on it, while the Danish delegation said that a final decision on participation in the project must await the findings of a review of Denmark’s policies for international

cooperation in science. As for participation by Norway and Sweden, these countries are prepared to back plans which entail an expenditure no greater than the 1,124 million Swiss francs that was first envisaged when the new proposals were drawn up last April.

The machine will be built underneath the Switzerland/France border next to the site of the present CERN 28 GeV proton synchrotron, which will be used to feed protons into the accelerator. The accelerator tunnel itself will be 2.2 km in diameter, bored through rock, and it will be essentially the same project that was first mooted last April by Dr John Adams, the director of the project. The beauty of the plan is that it removes at one blow the bitter disputes about where to site the machine and it also allows much greater flexibility in design. But by far its most powerful trump card is that it is about one third cheaper than the original design.

The idea is that the machine would first be built to a capacity of 150 GeV by using only half of the proposed magnets for bending the proton beam. The remaining magnets will therefore be installed at a time when it should be possible to assess the viability of superconducting magnets, and three choices will be open to the planners. The remaining magnets could either be of a conventional design, to give a machine of 300 GeV capacity, or they could be superconducting, to give a 400 GeV machine. Alternatively, if the original magnets were also replaced by superconducting magnets, the capacity of the machine may be as high as 800 GeV. The crucial decisions on magnet design will have to be made early in 1974, by which time the 150 GeV machine should be ready for operation. If it is decided to go straight to the 300 GeV machine using conventional magnet technology, this could be completed by the end of 1976.

This flexibility in design would have been lost if the original plans for the machine were adopted. The accelerator would also not have been linked to the 28 GeV facility in Geneva, and there was considerable dispute among the member countries about the ideal site for the project. The disagreement about the siting of the machine was sharpened by the high costs of the project—about 1,900 SF—and in 1968 the British government decided, against the advice of the Council for Scientific Policy, that it wanted no part in the project. This decision caused considerable heart-searching among the other member countries, and a cheaper, less satisfactory and watered down version was proposed. Agreement was, however, not obtained for this proposal, and the present plans were put forward just as it seemed that the project was unlikely ever to get off the ground.

The decision to go ahead with the

accelerator will have major implications for high energy physics in Europe (see page 594), but it will certainly not leave the domestic programme for elementary particle physics in Britain entirely unscathed. The British contribution to the project will work out at an average of about £3 million a year for the next eight years and this will be taken from the budget of the Nuclear Physics Board of the Science Research Council. The board pointed out in the annual report of the Science Research Council that “the sacrifices that must be envisaged to achieve the 300 GeV objective have sharpened”, but since then the proposed budgets of the research councils have been cut by the government, and the effects of entry to the project are likely to be even more keenly felt.

One consequence is that the Nuclear Physics Board has not sought funds for any major domestic facility over the past few years, and the growth in academic manpower has been held in check. If there is any more slimming to be done in elementary particle physics in Britain, the SRC is being coy about where the cuts are to be made. It seems, in any case, that there is little likelihood that the number of British particle physicists will be increased, and the scientists at the Rutherford high energy laboratory and at the Daresbury electron facility will be able to breathe more easily when the SRC makes known its thinking about domestic high energy physics.

CHEMISTRY

Policies for Change

A HALT in the rate of growth of research studentships in chemistry and more flexible postgraduate studies are likely to be the chief changes in the policy of the Chemistry Committee of the Science Research Council in the next few years. This means that after a sharp increase—35 per cent between 1967 and 1969—the total output of PhD graduates from chemistry departments in Britain will remain static at just over 850 a year for several years. But even this strong pressure on the brake will not alter the situation in which more PhDs are being produced than are needed for research and teaching, and the chemistry committee of the SRC will therefore view broader and more flexible courses of study with some favour when it shares out its funds for student support. This indication of the SRC’s policies for postgraduate education is contained in a review carried out by the chemistry committee (*Chemistry—a review of the policies and activities of the Chemistry Committee of the Science Research Council*, available free from the SRC), and the committee is no less explicit in its statements of policy for supporting research in chemistry.

Sticking closely to the policy of selectivity as outlined in the annual report of the SRC for 1969-70, the chemistry committee has been devoting some 20 per cent of its £1.5 million for research to selected areas, and distributing the remainder to "any spontaneous proposal judged to be of high scientific merit". Chief beneficiaries of this policy of selectivity have been polymer science and enzyme technology, and the committee has recently invited applications for research support in organometallic chemistry and photochemistry. Possible economic benefits are obviously at the back of the committee's mind when it designates areas for selective support but, although the committee pays lip service to the concept of innovation in the chemical industry, there is little evidence in the report that the committee seeks out and supports research of an unashamedly commercial nature.

As for future patterns of selective support, the committee singles out colloid chemistry as a likely candidate and has set up a panel to survey the subject. Nevertheless, "at this stage it is by no means clear that the committee will decide to give selective support to this subject", the committee warns. Whatever the panel's verdict, the committee says that it requires more information on the success of its support of photochemistry and organometallic chemistry before venturing into similar policies and, in any case, no more than one fifth of its funds should be devoted to selected areas.

While there are few major changes in the offing in the pattern of support for research, support of postgraduate training in chemistry seems unlikely to remain unchanged. As far as the SRC is concerned, the emphasis is now going to be on more flexible courses. The committee has calculated that there will be no substantial increase in the number of chemistry graduates at first degree level in the next few years, and, if present policies are not changed, that the growth in the output of PhD chemists is also about to flatten off at about 860 a year. The SRC supplies the largest source of support for postgraduate studies in chemistry (about 530 a year), and the chemistry committee suggests that the total number of SRC research studentships available to chemistry departments should not be substantially changed in the next few years.

To support this policy, the chemistry committee has carried out a brief survey of the job market for postgraduate chemists and it comes up with the finding that there will be about 870 jobs a year available for PhD chemists, assuming that about 120 immediately go abroad. But the committee is quick to point out that only about 700 of these jobs require a strongly research-oriented education in chemistry, and there is

therefore some room in the system for experimenting with more flexible courses. To be sure, the SRC has already made some changes in its awards policies—in 1967 the Cooperative Awards in Pure Science scheme was introduced and in 1969-90 SRC studentships in chemistry out of a total of 514 were awarded to industrially linked projects under this scheme. The committee is now, however, casting an approving eye on the Swann-type PhD courses with a strong core of research training and further study in other areas, and it puts the ball firmly in the universities' court by saying that it wishes "to encourage departments to propose new schemes along these lines, to provide a broader training both for the convinced researcher and for the man whose subsequent career is not likely to be concerned with research".

The chemistry committee also believes that there should be provision in the award of studentships for postgraduate students to change their course of study. The problem at present is that students accepted for PhD courses have little chance to change their studies because they would be likely to lose their grant. The universities themselves are also unwilling to admit that a wrong choice was made if a postgraduate student does not reach the standard expected of him. The answer, the chemistry committee suggests, may be to allow students to spend the remainder of their award on some other form of

training, for example a diploma in management studies. Under such a scheme, a postgraduate student would be able to end up with two different qualifications—an MSc and a diploma. This scheme is at present being looked at by the committee and it seems likely that it will be met with approval.

The publication of this review of the policies of the chemistry committee is a welcome step away from the obsessive secrecy that has characterized much of the workings of the research councils in the past. It is certainly tangible evidence that the SRC intends to take seriously its intention not to hold its cards quite so closely to its chest, and other research councils would do well to follow suit.

COMPUTER POLICY

Software Firms Boosted

IMPORTANT changes in government policy toward the computer industry were revealed last week. Representatives of the Civil Service Department (CSD) told a subcommittee of the Select Committee on Science and Technology that the role of their department is shifting, and a new attitude to the software industry, which marks a significant change from that during the Labour government, is emerging. At the same time the CSD's representatives, ably led by Mr A. A. Creamer,

Table 1 Computers in Use in Government Departments at December 31, 1970
Number and series of computers used by departments, the hardware cost and specialist staff employed

Department	Number of computers	Number of computer series	Cost (£'000)	Systems analysts and programmers (March 1970)
Agriculture, Fisheries and Food	4	3	1,189	66
Aviation Supply	28	11	2,982	67
Central Statistical Office	1	1	48	6
Customs and Excise	1	1	317	67
Defence (Navy)*	48	17	4,254	973
(Army)	25	7	3,906	
(Air)*	29	8	4,321	
(Central)*	14	5	2,502	
Education and Science	2	2	361	61
Employment	2	2	708	85
Environment	13	6	1,998	207
Export Credit Guarantee Department	1	1	64	6
Foreign and Commonwealth Office	2	1	59	10
Health and Social Security	11	4	4,619	335
Home Office/Metropolitan Police	4	3	626	111
Inland Revenue	5	3	869	152
National Savings	3	1	1,779	104
Office of Population Censuses and Surveys	2	2	382	69
Ordnance Survey	1	1	94	12
Paymaster General	1	1	460	22
HM Stationery Office	4	3	1,142	89
Trade and Industry	25	14	5,351	162
HM Treasury	1	1	176	—
Scottish Office	6	4	618	75
Two departments without installations	—	—	—	30
Total	233		38,805	2,709

* Including some used for flight and training simulation.

gave the latest figures for the numbers of computers and associated staff in government departments (Table 1). But the sub-committee, and the civil service witnesses who have been appearing before it, are obviously hamstrung by having to wait for Mr John Davies or one of his colleagues to come down from the mountain with the promised ministerial statement on the support for the British computer industry.

The CSD has taken to heart comments made before the Select Committee last year that the government was relying too much on its own internal programming resources in its assessment of government use of software. The witnesses revealed that the volume of business placed with outside software houses will now rise from £570,000 in 1969/70 to more than £1 million in 1970/71 and possibly to more than £1.5 million in 1971/72. But, like the other witnesses who have appeared this year, the CSD thought it would be even harder to distinguish between British and foreign software for the purposes of giving preference than it is to say which computers can be called British. Mr Creamer also said that ICL has less software available than American companies, but what they have is good and fulfils the government's requirements.

Apart from doctrinaire reasons, it looks as if one of the explanations for this significant shift in policy which will delight the software houses is that the government is having difficulties in training and keeping systems and programming staff.

As things stand, however, ICL continues to be the apple of the British government's eye in the hardware field. The CSD witnesses revealed that in the year ending on March 31, they expect 50 per cent of large computers and 86 per cent of small computers for the government to be bought through single tender contracts, and ICL will be the beneficiary with the exception of one or two small orders to Honeywell and IBM. In the same period up to March 31, the government will place £18,189,000 worth of orders for administrative and general purpose computers, of which £16,543,000 worth will be bought from ICL. But it seems that the government has no intention of boosting ICL further by ordering computers in bulk. Last year the managing director of ICL told the Select Committee that his company had never been asked for more than four of a particular type of computer at once, whereas the United States government sometimes purchases computers in large batches to the benefit of American companies. According to the CSD witnesses, however, the British government has not been offered a good enough discount to balance the disadvantages of bulk ordering.

Since last year when the CSD defined itself as the central coordinator which ensures that government policy on the use

of computers within departments is correctly applied, there seems to have been a devolution of responsibility to the departments themselves. Instead of providing detailed support to the departments, CSD staff are being redeployed "to a more active role of planning, proposal of common policies and promotion of technical developments of common interest". This has been made possible by the growing competence of the departments. In cases where departments still need help the practice now will be to call in the computer service industry.

Sakharov's Rights

from our Soviet Correspondent

DR ANDREI SAKHAROV, the Russian physicist and campaigner for human rights, has been told by the Procurator General of the USSR, Roman Rudenko, that he must either disband his unofficial "Committee for Human Rights" or else register it with the state. Dr Sakharov, well known already for his appeals of June 1968 and April 1970 for greater academic and personal freedom, founded his committee last November. The original members were Dr Sakharov himself, Valerii Chalidze and Andrei Tverdokhlebov. From the beginning, the committee stated that it would have nothing to do with any foreign or domestic organizations that were anti-Soviet.

According to Soviet law, any organization, whatever its aims and activities, must be registered. When founding the committee, Dr Sakharov announced his willingness to comply with this regulation. It seems, however, that for three months the official attitude to the committee has been ambivalent—whether to approve it and thus tacitly to admit the need of such an organization, or to ban it and thus give evidence of such a need.

The new move by Procurator-General Rudenko seems designed to bring matters to a head. Official recognition is hardly to be expected, yet it is difficult to imagine Dr Sakharov either abandoning his human rights campaign or discrediting himself by putting himself outside the law. So far, his appeals have always been based on the proposition that greater personal and academic freedom can only be to the benefit of the Soviet Union; his dissent, he maintains, is motivated by loyalty to his country. It would be ironic, indeed, if that very loyalty should now put him outside his country's laws.

Parliament in Britain

NRDC

MR JOHN DAVIES, Secretary of State for Trade and Industry, said that a review is being carried out of the arrangements for the exploitation of inventions resulting from public research and the support by the National Research Development Corporation for the development and exploitation of inventions from other sources. This review is being undertaken by Mr Docksey, formerly general manager of the research and technical development department of British Petroleum Ltd, and it should be completed well before the end of this year. (Written answers, February 17.)

Pollution and Sewage Disposal

THE government intends soon to announce its conclusions on the chief recommendations of the Working Party on Sewage Disposal. Announcing this, Mr Peter Walker, Secretary of State for the Environment, said that the proposal for combining water authorities with sewage authorities has been considered by the Central Advisory Water Committee, and this body has recently completed a report of its findings.

Asked by Mrs Kellett about the progress of his review of the effects of all forms of pollution, Mr Walker said that he is reviewing the whole question of pollution of rivers and seas. (Written answers, February 17.)

Students' Grants

MR WILLIAM VAN STRAUBENZEE, Under Secretary, Department of Education and Science, said in reply to a question from Mr Kenneth Marks that it would cost £35–40 million in the current academic year to abolish the parents' contribution to grants for students in higher education. Mr Marks also asked the Secretary of State for Education and Science whether she will introduce legislation to extend mandatory grants to students on full-time Higher National Diploma courses, and also whether she will set up a working party to examine the question of parental contribution to student grants. Mrs Margaret Thatcher promised that both these questions will be considered during the current review of grants. (Written answers, February 22.)

CS

MR RICHARD SHARPLES, Under Secretary at the Home Office, said that the committee under the chairmanship of Sir Harold Himsworth which is looking into the effects of the use of CS in Northern Ireland will not now be reporting until about the middle of this year. It was originally hoped that the committee would have reported last autumn, but it is still taking evidence. (Written answers, February 18.)

NEW WORLD

Nixon and Kennedy peddle Rival Cancer Cures

by our Washington Correspondent

THE proposal to infuse additional hundreds of millions of dollars into cancer research has become the subject of political rivalry between President Nixon and Democratic Congressmen led by Senator Edward M. Kennedy. Cancer researchers, interested only in seeing which group will outbid the other, are encouraging the contest with virtual assurances that a cure for cancer can indeed be bought if only the investment is sufficiently substantial. Beneficiaries of the new largesse—Congress, it seems, will be concerned to debate only its size—will include cancer research centres certainly, the wider field of biomedical research probably and cancer sufferers possibly, since nobody can be sure that the new funds may not perhaps hasten by a brief interval the cures for some kinds of cancer.

The proposal surfaced last December with the report of a panel of consultants commissioned by Senator Ralph Yarborough which advocated the setting up of a national cancer agency, separate from the National Institutes of Health, and funded at the level of \$1,000 million a year. The proposal was adopted in outline by President Nixon in his budget message last month, in which he earmarked a fund of \$100 million for cancer research in addition to the \$230 million budget of the National Cancer Institute for the financial year starting this July (see *Nature*, 229, 292; 1971). In his health message to Congress last week, Mr Nixon made slightly clearer his plans for the disposal of these funds; rejecting the idea of a separate agency, the President said a Cancer Conquest Program would be set up in the office of the Director of the National Institutes of Health. The Program will have a director (yet to be named) and a new Advisory Committee on the Conquest of Cancer, but the precise relation between these and the director of the National Cancer Institute with its National Advisory Cancer Council remains obscure. Meanwhile Senator Kennedy, who has succeeded the defeated Yarborough as chairman of the Senate's health subcommittee, introduced on January 26 a resolution calling for implementation of the consultants' panel proposal, though with an anticipated maximum budget of \$600 million a year, compared with the \$1,000 million income advocated by the panel.

Chiding the President for the attempt to steal his clothing, Kennedy remarked in introducing the bill that "Now that President Nixon has joined us in our commitment to the goal (of conquering cancer), I am hopeful that Congress and the Administration will act rapidly to complete the action that has been so well begun."

Although Mr Nixon has certainly joined the cancer crusade, he and his advisers have prepared a different and seemingly more intelligent goal than that of Senator Kennedy and his panel. Much of the difference in outlook that has so far emerged between the two groups stems from what was the major argument of the Yarborough panel's report, the belief that the planning and programming techniques developed by NASA and the AEC for applied projects could fruitfully be brought to bear on cancer research, given an appropriate size of effort.

The idea is one that has little appeal for most basic researchers, and its usual advocates are systems analysts who have gained their experience with applied projects, some of whom are fond of arguing from the premise that there is no clear dividing line between pure and applied research to the conclusion that there is no distinction between the two. The National Cancer Institute, however, is one place where the application of planning techniques to basic research

has a firm intellectual foothold, and it may be that the Yarborough panel of consultants gained some of their ideas from this source.

The analogy of conquering cancer by the same methods used to get to the Moon is at any rate one that is easy to sell to politicians. "The time has come," Mr Nixon said in his State of the Union address last month, "when the same kind of concentrated effort that split the atom and took man to the Moon should be turned toward conquering this dread disease". The same words were mouthed by Senator Kennedy in introducing his Conquest of Cancer bill: "The bill I am proposing will establish an independent agency . . . modelled along the lines of NASA which succeeded so brilliantly in reaching our goal of landing a man on the Moon in the decade of the sixties." And Congressman Cornelius E. Gallagher, introducing a similar bill into the House of Representatives on January 22, asked for the "piddling sum" of \$650 million a year for the next ten years (at the end of which, presumably, cancer would be vanquished) to be "controlled and directed by a National Cancer Authority which would have the same absolute direction of the cure and control of cancer that the National Aeronautics and Space Administration had over our conquest of space". The recent intellectual history of cancer research in Congress would not be complete without mention of the resolution introduced by Congressman John J. Rooney and passed by the House without dissent, that the conquest of cancer should be completed by 1976.

While Congressmen have remained content to regard the cure of cancer as a problem equivalent to the Apollo project, a thesis of which cancer researchers have done the minimum to disabuse them, President Nixon has of late been better advised. In his health message he explicitly denied the man-on-the-Moon theory of cancer he had promulgated in the State of the Union speech less than a month earlier. In the space programme, Mr Nixon remarked last week, "the challenge was technological; it did not require new breakthroughs. Unfortunately this is not the case in biomedical research at the present time; scientific breakthroughs are still required and they often cannot be forced, no matter how much time and money is expended".



President Nixon.



Senator Kennedy.

Having repudiated the Apollo analogy, the President went on to justify the new cancer initiative by his belief that new breakthroughs in cancer are imminent.

A possible reason for this shift of emphasis may have been the soundings taken by the Office of Science and Technology, which would presumably have sensed a certain antipathy among the scientific community towards the man-on-the-Moon theory of cancer. At any rate, to herald the Administration's abandonment of this idea, the President's Science Adviser was dispatched to Chicago a week before the President's health message. In the course of a speech to the Association of American Medical Colleges, Dr Edward E. David explained not once but on four separate occasions that what the President had really meant in saying conquering cancer was like getting to the Moon was in fact that the two goals differed considerably. ("The President clearly recognizes the subtleties behind this statement" was the way David put it.) The nature of cancer research, David said, "presents a stark aspect with Apollo and nuclear energy. Indeed we do not believe in an AEC or NASA for cancer".

David's speech constitutes an important reinterpretation of the Administration's attitude not only on cancer research but also towards the biomedical community at large, for whom David had some highly conciliatory remarks. It would be wrong to set up a separate cancer agency outside the National Institutes of Health (another major difference between the Nixon and Kennedy proposals) because, David argued, the cancer problem straddles virtually all the life sciences and hence, he implied, all should benefit accordingly from infusion of funds. "The President is also aware that this new venture must not be undertaken at the expense of the broad base of scientific research. We must

maintain the vigour, diversity and sparkle of biomedical research".

David also went out of his way to recognize the concern of the biomedical community about the fellowships and training grants administered by the National Institutes of Health. Although these are budgeted to remain constant next year, they reportedly escaped the knife of budget pruners only by a narrow margin. The President does not take a dogmatic stance about these grants and is waiting for the completion of an NIH study before deciding what arrangements to make for the support of students and trainees in the life sciences. "We welcome your voice in the debate over this issue," the Science Adviser told his Chicago audience, promising that "we will not move precipitously or capriciously but we need courageous assessments on your part. By courageous, I mean assessments which can lead to change where it suits national objectives".

David's address has been well received in the scientific community, in which he seems to have won wide support for Mr Nixon's initiative both outside and within the ranks of cancer researchers. "David's remarks were pretty sensible," was the reaction of one biologist last week. "I thought David's speech was splendid," said Professor Sol Spiegelman, director of the Columbia University Institute of Cancer Research. "A lot of us were against setting up a separate cancer agency divorced from the life sciences—David put it as well as a lot of scientists would".

Members of David's office are concerned to stress that they found a consensus of opinion among life scientists that this is a propitious moment for launching a new effort on cancer. Another factor behind the office's support of the proposal seems to be the feeling that this is a test project to see how well basic research can be harnessed to the problems of society, because cancer encompasses so much of modern biology the new effort cannot help having wide ramifications throughout the life sciences, but the Office of Science and Technology does not seem to have given attention to the specific aspects of research that justify the proposed new investment, regarding this as a matter to be decided by the scientists directly involved.

Dr Robert Q. Marston, director of the National Institutes of Health, said last week that while he had "no intention of using these funds other than as the President has indicated—to focus on cancer research—there are many areas of biological research directly related to the cancer programme".

Obvious research fields in which to concentrate the new support include viral oncology, cancer chemotherapy, chemical carcinogenesis and immunology. The extra funds will allow the National Cancer Institute to fund a larger pro-

portion of its research applications (last year only half the applications were approved, and of these 40 per cent of continuing projects and 10 per cent of new applications were funded). But Marston said the President's instructions were for the NIH to support not only individuals but also the more highly directed cancer programmes, to which the National Cancer Institute already devotes 40 per cent of its funds. "Both the President and the Yarborough panel recommended that we utilize modern management techniques in the cancer programme".

The Yarborough panel was in fact doing scarcely more than tell the NCI to do more of what it does already, since under the leadership of its director, Dr Carl G. Baker, the institute has probably acquired more experience in applying modern management techniques to research than any other members of the NIH. Formerly the chief of the NCI's programme planning section, Baker, on becoming acting director of the NCI, appointed to his old job a non-scientist with experience in managerial and planning techniques, Mr Louis M. Carrese. Formerly vice-president for management with the Frederick Research Company, an organization specializing in military systems and analysis, Carrese turned down offers from NASA and the Department of Defense to join the NCI in 1962.

Carrese believes the most fruitful opportunity for planning cancer research lies in the borderland between basic and applied research. Research, he says, should be defined in terms of specific objectives, such as particular human cancer problems, not conducted on an open ended basis. With Baker as co-author, Carrese has said (*Management Science*, 13, B-420, 1967) "a project judged to be excellent from a scientific frame-of-reference does not necessarily mean that it is of strategic significance from the programme standpoint".

Two of the programmes designed on the basis of this approach are the Special Virus Leukemia Program, now the Special Virus Cancer Program, and the Cancer Chemotherapy Program. A notable success of Carrese's methods is the recent demonstration by the former programme that none of the 31 adenoviruses cause cancer in man, an important result attained in only nine months' work. The Cancer Chemotherapy Program also has its successes, having discovered and taken through to the clinical evaluation stage nine new chemotherapeutic agents of use against various kinds of cancer and evaluated 30 others. These drugs have certainly helped to prolong the lives of many cancer patients, but apart from the special cases of Burkitt's lymphoma and choriocarcinoma, cancers which are uniquely susceptible to chemical agents, the programme has not brought a cure for cancer any nearer, despite the \$330

million that it has absorbed since it began in 1955.

Outside the immediate field of cancer research, there is apprehension that too large a proportion of the additional funds in the offing may be devoted to plannable research and too little to basic research which alone can afford a fundamental solution to the cancer problem. "At a certain level the new initiative is a disaster," one eminent biologist said last week, "since three-quarters of the relevant work for cancer is not being done in the name of cancer research. I think the people at the NCI will have to use their heads not to pilfer it all away. If they spend \$50 million on searching for a virus in breast cancer, or providing electron microscopes in Nebraska, or funding research in cancer centres as a form of psychiatric care for doctors to give them the impression of doing research, then they're going to get nothing for their money."

This gloomy view of the hard road ahead is not shared inside the National Cancer Institute, and indeed Baker, in testimony before the House Appropriations Committee on April 23 last year, stated, "there are many scientifically based reasons for believing that not all but most cancer might be preventable if we are willing to make the investment". This view is subscribed to by other cancer researchers, more than 600 of whom endorsed the resolution introduced last month into the House of Representatives by Congressman Gallagher, calling for a NASA-type conquest of cancer. The 600 cancer researchers subscribed in particular to this statement: "We further express our conviction that with the level of funding and the magnitude of commitment authorized under the Gallagher resolution, cancer can be cured and controlled." It is little wonder that outside the ranks of cancer researchers there are fears of a backlash against all kinds of science from a public conditioned to believe by both politicians and scientists alike that a cancer cure is as attainable as the Moon.

Udall Praises NAS

by our Washington Correspondent

THERE was praise from an unexpected quarter for the National Academy of Sciences at the hearing held last week by the Department of the Interior on the proposed construction of an oil pipeline across Alaska. Stewart L. Udall, former Secretary of the Interior under the Kennedy and Johnson administrations, criticized the department's recent report recommending in favour of the pipeline and blamed it for having failed to seek advice on the matter from such "superior outside consultants" as the National Academy of Sciences.

Udall, who is head of an environmental consulting agency, known as the Overview Group, last referred to the academy in a speech delivered to the AAAS meeting in Chicago last December. On that occasion he assailed the academy for having failed to speak out earlier and move vociferously in defence of the environment, calling it a puppet of government that only gave the answers it was asked for. These remarks provoked a sharp response from the president of the academy, Dr Philip Handler, who countered that Udall had wholly ignored the academy and its reports on the environment during his secretaryship; "Udall seems to have discovered the environment after he left his post as Secretary of the Interior," Handler said (*Nature*, 229, 151; 1971). Now, it seems, Udall has discovered the academy in a fresh light; his Alaska hearing speech sounds quite close to an apology.

COMPUTERS

Honeywell's New Range

THE recent announcement by Honeywell of a new range of computers implies that the company's acquisition of the business computer interests of General Electric (US) has already paid dividends. Honeywell claims that its new '6000' computers, which are closely related to a series which was nearing production at General Electric before the merger, will give at least 15 per cent more computing power than the IBM machines. And if the IBM policy of "unbundling" (that is, charging separately for software, maintenance and so on) is fully taken into account, the advantages of the Honeywell range could turn out to be much greater. The larger members of the new series also seem to have considerable advantages in computing power over the largest of the ICL '1900' series; the most powerful of the System 4 series made by ICL (the '4/72') is equivalent to the middle members of the '6000' family (the '6030' and '6040'). Honeywell obviously hopes to increase significantly its share of the British market but the company would be the first to admit that, in the public sector at least, it will have difficulty unseating ICL from its entrenched position.

Three members of the '6000' series have been specially designed for a mixed scientific and business workload but the other three can offer useful increases in computing capability for customers who will principally be using COBOL, the business language. Honeywell claims that the new series is the first to operate in all the four computing "dimensions", remote and local batch processing, time sharing and transaction processing (of which a good example is the storage of medical records). The four largest systems will also be available with as many as four central processors linked together in such a way that a fail-safe situation is achieved as well as increased throughput; the failure of one processor will no longer have a catastrophic effect.

Programs written for the 6000 series will be compatible with the smaller Honeywell 600 series, but compatibility of peripheral equipment with models made by other companies remains something of a thorny problem. At least one step in the right direction is the adoption of the COBOL programming language by the American Standards Institute as the recommended language for business machines.

Forecasts of the burgeoning state of the computer industry suggest that the value of computers installed throughout the world will double in the next five years to a staggering £31,000 million. With a ten per cent share of this market, Honeywell is well placed to take advantage of the boom, but the company will have to go a long way to make much impression on the dominance of IBM.

Salaries of US Scientists in 1970

Scientific and Technical Field All fields (in dollars)	Lower decile 9,500	Lower quartile 11,900	Median 15,000	Upper quartile 19,100	Upper decile 24,500
Chemistry	9,600	12,000	15,300	19,200	24,000
Earth and Marine Sciences	10,000	12,000	14,900	18,400	23,100
Atmospheric and Space Sciences	10,000	12,700	15,200	18,400	22,300
Physics	10,000	12,000	15,900	20,000	25,000
Mathematics	9,000	11,000	14,300	19,200	25,000
Computer Sciences	11,800	13,600	16,500	20,000	24,000
Agricultural Sciences	8,800	10,300	12,800	15,800	19,500
Biological Sciences	8,700	11,300	15,000	20,000	26,100
Psychology	10,500	12,300	15,000	18,500	23,700
Statistics	11,500	13,600	16,900	20,700	25,000
Economics	11,000	13,000	16,300	21,000	27,000
Sociology	8,500	10,400	13,000	16,700	21,000
Political Science	9,300	10,700	13,100	18,000	23,500
Anthropology	10,700	12,000	14,700	18,900	23,000
Linguistics	9,000	10,500	12,500	16,400	20,700

Source—National Register of Scientific and Technical Personnel, 1970.

NEWS AND VIEWS

Human Breast Cancer Virus?

IN mice, breast cancer (mammary adenocarcinoma) can be caused by a virus, the Bittner virus, which has an entirely characteristic and until now unique morphology. But on page 611 of this issue of *Nature*, Moore and his co-workers in Camden, New Jersey, Detroit and Bombay report the detection of particles, the morphology of which is identical to that of the Bittner virus, in many samples of human milk. The implications of this enthralling observation must be obvious to everybody—these particles in human milks may well prove to be the causative agents of human breast cancer, human breast cancer viruses, which can transform target cells in breast tissue when those cells occur in particular hormonal environments. In other words human breast cancer, like the murine disease, may well be initiated by a virus but promoted by humoral factors, in particular sex hormones.

Moore and his colleagues have detected this particle in seven out of one hundred and fifty-six samples of milk from Philadelphia women with no history of breast cancer in their families, in six out of ten milks from American women whose near female relatives had the disease and in eighteen out of forty-six milks from Parsi mothers living in Bombay. Although the size of the sample of milks from American women belonging to families with a history of the disease is small—no doubt because of the logistical problems of locating such women in lactation—the 60 per cent incidence of virus can hardly on that account be dismissed as insignificant. Similarly among Parsi women in Bombay, members of an inbred community of about 80,000 descended from Persian Zoroastrians who fled from Persia to escape religious persecution in the mid seventh century AD, the age adjusted incidence of breast cancer is at least 1.7 times that of the entire female population of Greater Bombay. And 39 per cent of the samples of Parsi milks contained detectable amounts of virus.

It seems likely therefore from these first data that more extensive samplings of milks from women of various categories and communities will reveal a correlation between high incidences of this virus-like particle in milks and individual risk of breast cancer. The correlation is unlikely to prove simple, however, for although breast cancer is more common among Parsis than other Bombay women, the age adjusted incidence of the disease is greater among English and Norwegian women, for example, than among Parsis. As with its murine counterpart the human milk virus may prove to be necessary for breast cancer to develop but not a sufficient factor to cause the disease.

Proof that murine breast cancer can be caused by the Bittner virus involved a fascinating but protracted series of inbreeding and cross breeding experiments; these established that some factor in milk transmits the cancer. Subsequent extensive investigations of mouse milks were made in an attempt to determine the identity of the agent and only recently have these culminated in the proof that one specific particle—the Bittner or mouse mammary tumour virus—is the aetiological factor. Although this virus is usually transmitted from mother to offspring in

the milk rather than through the placenta or through the egg and sperm, it is significant that at least in some strains of mice the viral genome can apparently be transmitted in the sex cells.

Comparable breeding experiments with human populations are obviously out of the question and epidemiological statistics correlated with the results of screening tests for the human milk particle will no doubt prove, as usual, to be only a contentious and inadequate substitute. Marshalling a body of experimental and therefore circumstantial evidence sufficient to convince the sceptically inclined that this human milk particle is indeed a breast cancer virus is likely to prove equally problematical. The sort of evidence that is needed will include proof that human breast cancer cells contain virus-specific antigens or viral nucleic acids, that the cancer cells produce the virus, that the virus can transform cells in culture or induce breast tumours in animals and, most convincing of all, evidence that it is possible to vaccinate against the virus and lower the incidence of the cancer as a result, always assuming the human virus is not transmitted until after birth. Each of these criteria is bound to be extremely difficult to establish, not least because it has so far proved impossible to find a cell which can be transformed by or supports the replication of Bittner virus and the human virus will probably prove to be equally fastidious. Bittner virus has to be assayed in mice; quantitative investigations of the human virus will depend on finding some susceptible animal or cultivated cell.

Apart from further investigations of samples of milk there are, however, several obvious experiments that might be done as soon as enough of the human virus has been collected. Tests can be made to see if the particles contain reverse transcriptases and attempts should be made to establish whether or not the human virus and the Bittner virus share a common intergroup specific antigen, for such a common antigen has been found among the various mammalian sarcoma and leukaemia viruses. It would also be worthwhile testing to see if antisera against the Bittner virus antigens inhibit the reverse transcriptase activity, if one is detectable, in the human virus; such an experiment involving sarcoma and leukaemia viruses of different species is already afoot. Further experiments along the lines of those reported by Charney and Moore on page 627 of this issue of *Nature* are also called for. They have incubated Bittner virus with sera taken from women who have had breast cancer or, as a control, normal women, and then assayed the tumorigenicity of the treated virus. They claim to detect a statistically significant neutralization of the murine virus by the sera of the cancer patients, although it is debatable whether or not great reliance should be attached to the differences between averages of such a limited set of data. Notwithstanding their limitations, however, these experiments indicate one approach to establishing the serological relationships, if any, between the human virus and the Bittner virus.

There remains, of course, perhaps the most important but thorniest job of all. We shall not be able to get to grips at the molecular level with the biology of the mam-

mary tumour viruses unless a susceptible cell which can be grown in culture is identified. There is no short cut. All the available cell lines will have to be tested.

But does the discovery of this virus particle in human milks have any implications for the treatment of what is after all the most prevalent cancer of adult females in many populations? It has to be admitted that in the short term there are precious few. Charney and Moore's suggestion that it might be possible to immunize against human breast cancer using the mouse virus as immunogen will cause more than eyebrow raising in many a tumour immunology laboratory. If the chief route of transmission of the human virus is through milk it might conceivably be possible to mount screening programmes for the virus in milks, the results of which might indicate cases in which breast feeding should be discouraged. And if the

baby's first contact with the virus is in its mother's milk it might just be possible to devise some immunotherapy. On the other hand, should the virus be vertically transmitted in the sex cells, as in some strains of mice, or by passage across the placenta, immunotherapy would almost certainly prove useless in the face of immunological tolerance. Indeed, the problems of dealing with any vertically transmitted virus disease are at present intractable. It remains, however, an article of faith among tumour virologists that an understanding of the cause of cancer should at least facilitate the design of tailor-made chemotherapeutic agents. That, and the possibility that a screening procedure for this human virus in milk might provide another parameter for the early diagnosis of breast cancer, provides a realistic perspective to these most exciting discoveries.

Bright Future for European Particle Physics

Now that the final decision to build a large proton accelerator in Europe has been taken, it is only natural to speculate about the steps forward which may be achieved in elementary particle physics during the next decade or so. Many physicists, however, will point scathingly at the apparent plethora of expensive high energy devices now working or planned throughout the world. How is it possible to justify on scientific grounds the construction of the intersecting storage rings at Geneva, the 200 GeV synchrotron at Batavia and now the accelerator at Geneva?

There is no one word answer to this, of course, but a number of justifications can be put forward. Both the existing CERN and Brookhaven machines have been producing protons of comparable energy (about 30 GeV) for more than ten years and one would have been forgiven for suggesting at their inception that there would be wastage of money and resources. As it turned out, nothing has been further from the truth and both laboratories are continuing to make maximum use of their available potential with few signs of repetition.

Experience with the CERN machine in particular should convince those persons who require a definite statement of scientific intent that not only is such a statement difficult to formulate but also it will almost certainly be changed out of all recognition as time passes. The CERN machine was conceived originally as a means of searching for the antiproton but the antiproton was discovered before it was even commissioned.

The intersecting storage rings at CERN must now be regarded very much as a window on the future; to a great extent the programme of research at the new accelerator will be determined by what is discovered with them. In fact, the decisions whether or not to increase the 300 GeV to 400 GeV and eventually to 800 GeV by adding and changing magnets may of necessity depend on the experiments at the storage rings.

Having made the point that all the best laid plans are likely to be modified by future events, there can be little harm in indulging in some crystal gazing. One of the chief questions which particle physicists would like to answer is not how, but why, some particles can be so successfully classified by the SU(3) and SU(6) group

theoretical approaches which have dominated high energy physics recently.

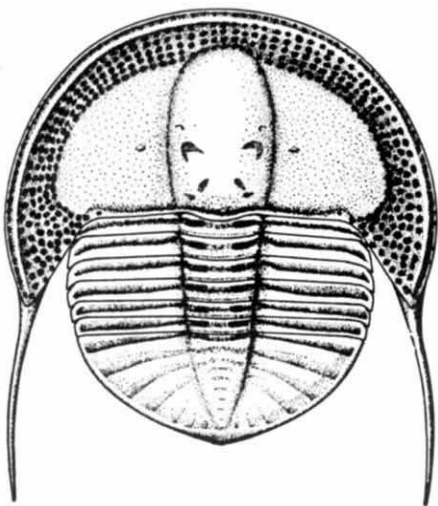
Some particles have been theoretically predicted—not always from SU(3) and SU(6)—but have not so far been detected experimentally. The discovery of these could well be an important contribution from the new accelerator. The controversial quark, in which most physicists find it hard to believe because of its non-integral electronic charge, is an obvious candidate for an intensive search; it may be, however, that the quark is discovered before the European accelerator comes into operation and, in that case, quark physics will become one of the important fields of experimental study at the accelerator from the beginning.

Many physicists have a much deeper and more intuitive belief in the intermediate boson which is thought to mediate the weak interaction (responsible for the decay of many semi-stable particles) in much the same way as the photon mediates the electromagnetic interaction. If it exists, this boson can almost certainly be produced in neutrino interactions and is being actively searched for in neutrino beams at accelerators throughout the world. Pairs of intermediate bosons can also theoretically be produced in proton-proton interactions and there is the distinct possibility that they may first be seen at the Geneva storage rings.

The Dirac magnetic monopole is yet another candidate for revelation by either the storage rings or the 300 GeV accelerator, but it has not excited sustained interest over the years and the interactions which might produce it are not really known. Its signature would be very characteristic, however, because its ionizing power at relativistic speeds is thought to be about 10^8 greater than any other charged particle.

Perhaps the most exciting advance will be a revelation of the structure of the nucleon. It is already clear from electron and neutrino scattering that the nucleon structure is granular and that the grains have a distribution of masses. Some theoreticians have explained this "granularity" in terms of the quark, and yet others have suggested that they are manifestations of new particles called partons. The situation is curiously similar to that in which Rutherford found himself earlier in this century.

TRILOBITES

An Australian Trinucleid

A new genus and species of trilobite—an extinct marine arthropod which flourished in the early Palaeozoic—has been recovered from Upper Ordovician siltstones near Parkes in New South Wales. According to K. S. W. Campbell and G. J. Durham of the Australian National University (*Palaeontology*, 13, 572; 1970), it is the first member of the family Trinucleidae to be described from Australia. They have given it the name of *Parkesolithus gradyi* and this figure shows their reconstruction which illustrates the trilobite's semicircular cephalon with its unornamented spines and the six-segmented thorax.

RODENTICIDES

The Search Continues

from a Correspondent

IN Britain, at least, some far reaching changes in the control of rodent pests are on the way, as a result of the development of resistance to anticoagulant rodenticides. Some of these changes were discussed at a symposium on rodenticides held by the Pesticides Group of the Society of Chemical Industry in London on February 15.

In the first contribution, Mr R. Scott (Royal Borough of Kensington and Chelsea) suggested that, besides resistance, the casual manner in which anticoagulant rodenticides were used was an important element in the complex of factors contributing to current increases in infestation by the urban house mouse. This theme was continued by Mr J. H. Greaves (MAFF, Pest Infestation Control Laboratory) (PICL), who pointed out that the apparently inexorable spread of populations of resistant rats which now occupy some thousands of square miles of agricultural land in Britain has arisen largely from the continued use of anticoagulants in the affected areas, a practice which has been unavoidable in the absence of alternative rodenticides that are equally safe and convenient to use.

Dr A. D. Martin (PICL) suggested

several physiological mechanisms in rodents which may be open to attack by particular classes of compounds. Among his favourites were new types of anticoagulants and antimetabolites of nicotinamide, but the list included drugs with immunosuppressive, hypoglycaemic and antihypocortisoid activities and many others. Two intriguing suggestions were that the target species might be presensitized or that rodenticides could be potentiated by the respective use of inducers or inhibitors of metabolizing enzymes. The problems, however, of developing basic ideas of this sort were vividly illustrated by further contributions which showed that relatively little progress in specific lines of research had so far been made. This research has included attempts to upset thermoregulation in the mouse (Mr R. A. Davis, PICL) and to remove the limitations of alphachloralose as a rodenticide (Mr J. O. Bull, Rentokil

Laboratories) through the use of a combination of compounds.

Dr P. B. Cornwell (Rentokil Laboratories) went on to describe an extensive series of experiments aimed directly at securing improvements in existing rodenticides through the application of microencapsulation techniques. He concluded, however, that though the principle might be valid, basic improvements in the characteristics of release of the microcapsules were needed to yield results of practical value.

The door was held open to a possible, if unpredictable, quick success by Mr F. P. Rowe (PICL), who described a screening project in which compounds submitted by industry are tested for rodenticidal activity on a confidential basis. Doubts were expressed about the immediate commercial prospects for new rodenticides, for resistance is not yet sufficiently widespread to create a major

Picking Up Chick Genes

WHEN an inert nucleus from a chicken erythrocyte is introduced by cell fusion into the cytoplasm of a different cell type derived from another species, it resumes synthesis of nucleic acid and chick specific proteins. Finding out how the chick genes are reactivated is, in itself, an exciting enough prospect, but in next Wednesday's *Nature New Biology*, Harris and his colleagues at Oxford take the technique a stage further by introducing genetic material from chick erythrocytes into nuclei of mouse cells.

The chick nuclei were introduced into the cytoplasm of mouse A9 cells by the now conventional means of inducing cell fusion with ultraviolet inactivated Sendai virus. The mouse cell strain lacked the enzyme inosinic acid pyrophosphorylase, but the chick cells were derived from birds which did not have this disadvantage. The hybrid cells were then grown up in a medium in which cells lacking this enzyme activity die.

Only cells in which the chick erythrocyte nucleus has been reactivated can therefore survive in this medium. But within three or four days of the cell fusion, the heterokaryons enter a mitosis during which the erythrocyte nuclei disintegrate. Any cells which survive after this time must therefore have a functioning chick gene for inosinic acid pyrophosphorylase, presumably located on a chromosome inside the mouse nucleus. The corresponding enzymes synthesized by mouse and by chick can be distinguished by their electrophoretic properties, so Harris and his colleagues were able to show that the survival of cells in the selective medium did indeed result from the synthesis of the chick-coded enzyme.

But looking at the chromosome constitution of the surviving cells showed that no chick chromosomes were present. This implies that during the disintegration of the chick erythrocyte nucleus, some of its genetic material has been incorporated into the mouse chromosomes. That there must be very little such chick material was shown by testing the cells for chick specific antigens on their surface; this is a very sensitive test indeed, and the genes which determine these antigens are widely dispersed on the chromosomes of the chick cell. No such antigens could be found on the surface of these cells, which implies that the extent of chick material picked up by the mouse nucleus must be very small indeed.

What is the state of the chick genetic material in the mouse nucleus? Is it integrated into the mouse chromosome or is there some other form of attachment? The rate at which the gene coding for inosinic acid pyrophosphorylase is lost from cells can be estimated by transferring cells into a normal medium in which the enzyme is no longer needed for survival, and then transferring to a medium which selects against cells which produce the enzyme. This gives an estimate of the number of cells that have lost the enzyme activity during growth in the normal medium. Normal mouse cells lose the enzyme at a frequency of less than 1 in 10^6 , but in the hybrid cells the frequency was 20 per cent.

This means that the chick genetic material has been only loosely integrated into the mouse cells. Harris and his colleagues have not yet shown conclusively that the chick genetic material is in the nucleus of the mouse cell, but it seems unlikely that it has remained in the cytoplasm.

new market. These doubts were reflected in the news that the World Health Organization is also sponsoring research on new rodenticides and they gave added force to the view that continuing support in the public sector is necessary for progress in this small but active and disproportionately important field of research.

RESERVOIRS

More Midges, More Fish?

INCREASING by artificial means the number of midge larvae in a reservoir seems a topsy turvy way of providing drinking water free of foreign bodies. Investigations by the Inland Fisheries Branch of the State of California Department of Fish and Game suggest, however, that midges and drinking water are not so incompatible as they might seem (*Fish Bull. Calif.*, No. 148; 1970). Midge larvae are important in the food chains of certain fish. Increasing the numbers of these larvae should therefore, in theory, provide more food for fish, and ultimately better fishing. If this can be done by a method of artificial destratification of the water, a practice incidentally which also improves the quality of water, the water authorities should be in business. It was an experiment which the California Department of Fish and Game thought worthwhile.

Midge larvae, together with tubificid worms, nematode worms and certain species of mollusc, are typical bottom dwelling animals of all freshwater lakes and reservoirs. But in summer months their distribution is limited and they may be absent from the deeper parts because the water there can become deoxygenated and the bottom muds are often toxic. This state of affairs is found particularly in lakes and reservoirs which are rich in nutrients (what limnologists call productive or eutrophic bodies of freshwater) and arises from a combination of physical factors.

In summer months when there is comparatively little wind to stir up the water, the upper layers warm up more quickly than the lower regions and a sharp division in temperature—a thermocline—is formed. Decomposition of organic matter in the deepest parts uses up the oxygen, and toxic materials accumulate in the mud at the bottom. At certain depths therefore the reservoir or lake becomes divided into a lower, anaerobic cool layer or hypolimnion and an upper, warm aerobic epilimnion. In a particularly productive reservoir in which a large part of the water is deoxygenated, the water is obviously not very suitable for drinking and abstractions can then be made only from the epilimnion. One solution is to destratify such reservoirs artificially by injecting compressed air and the California Department of Fish and Game has already

shown this to be feasible; it improves the quality of water by making the temperature and oxygen concentrations relatively uniform throughout the year. But how does destratification affect the bottom organisms such as midge larvae, which in a sharply stratified reservoir are presumably excluded from the toxic deep parts and therefore less available as food for fish? The department decided to investigate this problem in El Capitan Reservoir in San Diego County. The reservoir was destratified in 1965 and was not allowed to stratify again until 1967. The bottom organisms were sampled by dredging in 1964 before destratification and in 1965, 1966 and 1967.

During destratification midge larvae, oligochaete worms, nematode worms and clams rapidly invaded the deepest regions in summer and their total numbers increased dramatically. In stratified conditions in 1964, for example, midge larvae were practically absent below a depth of 10 m by July; in 1966 there were substantial numbers at 25 m or more. The oligochaetes and the nematode worms fluctuated in a similar manner.

It seems likely that a combination of factors—ample oxygen and food and warmer temperatures—led to the changes in the populations of bottom organisms, rather than oxygen alone. The El Capitan results certainly indicate that artificial destratification might retard or reverse natural eutrophication in such waters and make them less productive. This could, in theory, have a limiting effect on fish populations. On the other hand, changes in the distribution of food, such as midge larvae, and the better environmental conditions for fish in the hypolimnion in summer might more than counterbalance a minor decrease in productivity. This is a long term implication. Meanwhile, the California Department of Fish and Game is considering using artificial destratification in reservoirs like El Capitan as an alternative to heavy treatment with copper sulphate which is often used to remove algae and to make the water drinkable. This substance, it says, can have much more immediate effects on fish populations far worse than anything to be expected from destratification.

Another Biological Control Mechanism

MOST molecular biologists would agree that a given structural gene dictates the amino-acid sequence of a protein and that, given this sequence, the polypeptide chain will fold itself into the "native" structure. In the case of proteins comprising more than one polypeptide chain there is, of course, the extra stage of subunit assembly. In next Wednesday's *Nature New Biology*, M. Rosenberg presents some findings which indicate that subunit assembly can be tissue specific inasmuch that different distributions of lactate dehydrogenase (LDH) isoenzymes are observed in different tissues although the component subunits are the same. The LDH molecule is known to be tetrameric and isoenzymes arise from the fact that different subunits, A and B, assemble to give molecules of the structure A₄, A₃B, A₂B₂, AB₃ and B₄. If the assembly of equal numbers of A and B chains is random, then these forms will occur in the binomial proportions of 1 : 4 : 6 : 4 : 1.

In mammalian tissues there are usually five distinct isoenzymes although the distribution varies from tissue to tissue for a given animal. Rosenberg claims that this differential tissue distribution in mammals is explained simply by there being excess of one subunit over the other as a result of differential rates of synthesis of the two types of chain. In a number of fish, however, Rosenberg has found that there are only one, two or three isoenzymes and in fish with five isoenzymes the distribution is non-random. She was able to take a three isoenzyme mixture from the common

mackerel (*Scomber scombrus*) and dissociate and reassociate it *in vitro* to give all five isoenzymes. Their relative migrations in an electric field indicated that the three isoenzymes in the original mixture were A₄, A₂B₂ and B₄ and this was confirmed by immunochemistry. Rosenberg showed in similar fashion that two isoenzyme fish LDH was A₄ and B₄ and one isoenzyme LDH was A₂B₂.

The differential distribution of isoenzymes in different tissues of the same organism was well illustrated by the alewife (*Alosa pseudoharengus*) which had two, three and five isoenzymes in different tissues. Controls indicated that failure to observe the missing structures was not related to the fact that they were preferentially degraded in the extraction procedures.

Rosenberg concludes that the missing isoenzymes are absent because their dissociation rates are disproportionately high and that this could be a function of the different concentrations of ions, proteins and coenzymes in different tissues. Rosenberg's findings complement the statement by Jaenicke (in *Pyridine Nucleotide Dependent Dehydrogenases*, edit. by H. Sund, p. 70; Springer-Verlag, Berlin and New York; 1970) that the primary structure in conjunction with the specific solvent conditions is the major determinant of the three-dimensional structure up to the level of quaternary structure. The mode of subunit assembly is thus potentially a further source of control in biological systems.

PROTEIN SYNTHESIS

The Captive Messenger

from our Molecular Biology Correspondent

WHETHER the particles of rapidly labelling RNA and protein that have been seen in the cytoplasm of mammalian cells are fact or artefact is still regarded in the more sober quarters as an open question, and so indeed is their relation to the complexes containing messenger RNA that are released when polysomes are dissociated. That labelled RNA comes away in sizable particles of high buoyant density has been known for some time, but the possibility that the RNA picks up basic proteins when dunked in the cytoplasm cannot be disregarded. Such random association was indeed shown to occur last year by Baltimore and Huang.

The nature of the complexes present in rat liver polysomes has now been re-examined by Lee and Brawerman (*Biochemistry*, **10**, 510; 1971), who report as follows: Treatment with EDTA releases pulse labelled RNA in the form of a highly polydisperse population of particles. The same effect could be produced in other ways—by raising the pH at defined potassium and magnesium concentrations and by treatment with urea. Free messenger cannot be liberated by urea or by high ionic strength, and the particles differ in this respect from the non-specific, and presumably adventitious, complexes described by Baltimore and Huang. Treatment with sodium dodecyl sulphate, which is one of the most efficient reagents for breaking up complexes between proteins, is the only satisfactory method so far known for extracting the free messenger. The latter has a much smaller sedimentation coefficient than the complex, which moreover is the same no matter from which fraction of the broad sedimentation profile of the complex it has been extracted.

The question remains whether the associated material consists of proteins torn out of the ribosomes on dissociation, or of components that the messenger carries into the cytoplasm. The first and more obvious explanation is supported by an observation of Nolan and Arnstein, who found that a poly U messenger carries ribosomal protein away with it on dissociation of the ribosomes. On the other hand, Lee and Brawerman refer to work of their own, as yet unpublished, according to which ribonuclease-treated ribosomes, when exposed to EDTA, release that part of the messenger which is shielded against the nuclease, in uncomplexed form. They also report that in a similar mammalian system, the complexes are found after the ribosomes are allowed to run off the messenger.

It may be remarked that it has not even been properly demonstrated that the associated material is protein, and there is at this stage little that one can say about the possible purpose of this

luggage that the messenger seems to carry around the cell. Lee and Brawerman suggest that it is unlikely to be anywhere but at the end of the molecule if it is not to impede the translation process, and that it may be nothing more than a part of the cell membrane to which the polysomes are normally tethered. It will be recalled, however, that descriptions have been published of ribosomal proteins that attach the ribosome to the membrane.

Another unexpected feature of a eukaryotic messenger is reported by Gaskill and Kabat (*Proc. US Nat. Acad. Sci.*, **68**, 72; 1971). They have prepared rabbit haemoglobin messenger from polysomes, and examined it electrophoretically in polyacrylamide gels. In this medium it separates from various contaminants and degradation products and can be unequivocally identified by its labelling properties. There follows something of a leap of faith in that the authors

determine the molecular weight from the electrophoretic mobility in the gel. This method in general seems to give reliable results, but would be expected to fail for species with very different degrees of base-pairing from those of the standards in terms of which the calibration is set up. A graphic example of such an effect is to be found in a recent article by Groot, Aaij and Borst (*Biochem. Biophys. Res. Commun.*, **41**, 1321; 1970), who find that with mitochondrial RNA the measured molecular weight changes by 40 per cent relative to calibration standards, according as the measurements are made at 2 or 28° C. This reservation aside, however, Gaskill and Kabat's results at least suggest that the messenger is more than half as long again as it need be to code for the globin chains. This may relate to the battery of stop and start and perhaps other signals that Sanger and his colleagues found in the polycistronic R17 viral RNA.

Heterogeneity of Antigenicity in Malignant Cells

CANCER research wends a tortuous path reflecting the many basic uncertainties in our understanding of the genetic control of differentiation of metazoan cells. Relatively recently, studies in which malignant and normal cells were hybridized revealed that a malignant genotype could apparently be masked in the presence of a normal complement of genetic material (Harris *et al.*, *Nature*, **223**, 363; 1969). The same series of experiments suggested that certain malignant cells had the ability to hide the transplantation antigens of the normal cell constituent of hybrids. The inference from this second finding was that tumours which had been transplanted a long time could enhance their capacity to grow malignantly by effective reduction of antigenicity. Such a mechanism could be thought of as involving antigenic simplification by genetic deletion or, alternatively, a modification process could be implicated by which the activity of these genes, which determine the transplantation antigens, could be quantitatively reduced. Modifier genes are familiar to botanists as a common feature of the genetic changes involved in speciation.

A further set of experiments described in next Wednesday's *Nature New Biology* is relevant to this theme. Negroni and Hunter have amplified an earlier finding (E. J. Walls and G. Negroni, *Europ. J. Cancer*, **2**, 221; 1966) that a clone of cells, isolated from a polyoma induced fibrosarcoma, though itself non-malignant can effectively immunize against the growth of a similar but malignant cell population. The evidence is compatible with the notion that the non-malignant cell population is more antigenic than the malignant cell clone

but has a qualitatively similar antigenicity. Negroni and Hunter go on to show that malignant cell clones can be derived from the "non-malignant" cell line by selection with an immune antiserum (produced in C3H mice by immunization with the non-malignant cell lines). The same antiserum applied to certain malignant cell populations effectively reduced immunosensitivity among the survivors.

The phenomenon of tumour progression, by which is implied a change in growth potential with time, has been recognized for many years and a summary of its ramifications has recently been published (L. Foulds, *Neoplastic Development*, **1**, Academic Press, London and New York, 1969). It seems possible that the heterogeneity of antigenicity among malignant cell populations such as that described by Negroni and Hunter is an aspect of tumour progression and a singularly interesting corollary is that, if non-malignant variants could be selected and grown from among a tumour cell population, it is possible that they could be used as a means of immunizing against the truly malignant cells. It is also tempting to wonder whether the "non-malignant" characteristic which, according to the earlier information, involves a lack of the capacity to liberate virus in culture and normal contact inhibitory behaviour really is non-malignant. Would these cells which display such meek characteristics in normal adult mice betray a malignant nature in immunologically deprived recipients? If they did, it would be necessary to define malignancy as a state resulting from a particular tumour-host relationship; a long overdue alteration in immunologists' thinking.

STROMATEOID FISHES

Life with Jellyfishes

from our Marine Vertebrate Correspondent

THE stromateoid fishes are a widely distributed group of temperate and tropical marine fishes found in a range of depths in inshore and oceanic waters. Perhaps one of the best known, a member of the family Nomeidae, is the Portuguese man-of-war fish, *Nomeus gronovii*, which is found under the float of the siphonophore *Physalia* swimming actively among the toxin-laden tentacles. Their apparent immunity to the toxin produced by the stinging cells has aroused considerable interest, and one report suggests that they can survive as much as ten times the dose of *Physalia* toxin that would kill a fish of comparable size. In spite of this relative immunity *Nomeus* seems to avoid contact as much as possible with the tentacles. Many other stromateoids are known to similarly associate with jellyfishes and siphonophores.

Stromateoid fishes show marked changes during growth, and the body form of young fishes is often markedly dissimilar to that of the adults. The differences are not all external, however, for although most lack a swimbladder when adult, they possess a functional one as juveniles. Dr Michael H. Horn has discovered that in fourteen out of the fifteen recognized genera of stromateoid fishes the swimbladder regresses with age (*Breviora*, No. 359, 1; 1970). The exception is the largely coastal genus, *Pampus*, which seems to have no swimbladder at any age, and is believed not to associate with jellyfishes when young.

The swimbladder in these fishes is a hydrostatic organ and, even if small, provides a degree of buoyancy. During their young stages the skeleton is poorly ossified and the musculature may not be well developed, and thus the juveniles probably have a lower specific gravity than the adults, and even a small swimbladder will take them close to neutral buoyancy. The reduction of the swimbladder with growth is gradual, the sac diminishing slowly until it is completely resorbed.

The interest in these observations lies in their relation to the biology of these fish. In the American Atlantic coast butterfish, *Peprilus triacanthus*, the swimbladder has completely regressed by the time that the fish is 10 cm in body length, and it is at about this size that the young cease their association with jellyfish medusae. Butterfish smaller than this length swim by hovering close to the medusa, whereas larger specimens do not hover but swim continuously. The pectoral fins increase in size with age and are used extensively for propulsion by the larger fish. It

seems that continuous swimming with some propulsion by the pectoral fins is the general way of life for adult stromateoids.

Nomeus, the stromateoid which associates with the siphonophore *Physalia* in a more intimate and enduring way than its other relatives, retains a functional swimbladder at a greater length than other stromateoids. It is not known whether *Nomeus* remains with *Physalia* throughout its life, but specimens as large as 143 mm body length have been captured at the surface

with *Physalia* and possess a large swimbladder.

Horn's study shows that the possession of a swimbladder in the young stages could be a positive advantage to a fish which lives under jellyfish medusae, or among the toxin-laden tentacles of a siphonophore, floating at the surface. An ability to stay afloat efficiently and manoeuvre with nicety in such a microhabitat is as obvious an advantage to the small fish as the greater swimming capacity of adults living in deep water in the open ocean.

Carbohydrate or Protein in Transplantation?

Sanderson, Cresswell and Welsh suggest in next Wednesday's *Nature New Biology* that the antigenic determinants responsible for exciting immunological responses to tissue and organ grafts are predominantly carbohydrate rather than protein. Using human spleen tissue from individuals known to possess three quite distinct transplantation (histocompatibility) antigens (Bt 4, Bt 5 and Bt Walde), Sanderson *et al.* prepared glycoprotein fractions by digestion of cell membranes with papain and purification with the aid of chromatography and disc gel electrophoresis. These soluble materials, each with a molecular weight of approximately 45,000, were further digested with insoluble pronase and the resulting glycopeptides were separated from the bulk of the amino-acids and peptides by chromatography on 'Sephadex G-50'. A low molecular weight (probably 8–10,000) fraction with a very high carbohydrate content was obtained for each specificity and was found to be serologically active in that it inhibited the lytic action of the specific antiserum. The glycopeptides of this fraction had a restricted range of amino-acids which always included aspartic acid, serine and threonine—all of which are especially concerned with linking sugar to protein.

At first sight these data seem to be irreconcilable with the now widely held view that the specificity of the "strong" histocompatibility antigens—the antigens controlled in man by the HL-A and in the mouse by the H-2 locus—depends on the amino-acid sequence of glycoproteins. This notion stems largely from the work of Shimada *et al.* (*Proc. US Nat. Acad. Sci.*, **65**, 691; 1970), who analysed and compared tryptic digests of glycoproteins obtained from mice carrying two distinct H-2 specificities. Although 90 per cent of the peptides were identical, each preparation had some that were unique, whereas no detectable differences were found in the composition of their carbohydrate moieties (Nathenson, *Ann. Rev. Genet.*, **4**, 69; 1970). The weakness of these experi-

ments is that Shimada *et al.* did not subject their fractions to biological tests such as *in vitro* inhibition of antibody, and that the amino-acid differences found by them could be unrelated to the activity of immunodeterminants that may form only a very small portion of the glycopeptide molecules. Nevertheless their data, together with those from other laboratories, seem to implicate protein quite strongly. The carbohydrate hypothesis, on the other hand, derives support from the observation that mouse (Billingham *et al.*, *Transplant. Bull.*, **5**, 377; 1958) and human (Sanderson and Cresswell, in *Transplantation Antigens and Tissue Typing*, edited by Elves and Nisbett, p. 87; Oswestry Orthopaedic Hospital Management Committee, 1969) histocompatibility antigens can be largely inactivated by periodate treatment, and that there are serological cross-reactions between mouse H-2 antigens and pneumococcal polysaccharide type XIV as well as human blood group A substance (Brent *et al.*, *Brit. J. Exp. Pathol.*, **42**, 464; 1961).

In an attempt to reconcile their own data with those pointing to the role of protein, Sanderson *et al.* suggest that although the specific determinants may be composed of carbohydrate they are carried on a molecular peptide backbone that plays a crucial part in the spatial arrangement of the determinants and therefore, indirectly, in determining their specificity. This is an interesting idea which has already been considered in relation to the mouse H-2 antigens (Shreffler and Klein, *Transplant. Proc.*, **2**, 5; 1970), but further work is needed to test its validity. Will these low molecular weight glycopeptides prove to have biological activity other than the ability to inhibit antisera; for example, can they sensitize or induce tolerance? Whatever the answer, Sanderson *et al.* have made it clear that carbohydrate is not merely an accidental contaminant of histocompatibility antigens, and that it is likely to have a highly specific function.

NUCLEAR PHYSICS

Symmetric Fission

THE continuing competition to produce new nuclear species is providing more material for studies of the properties of fissioning nuclei, even though the pace in this branch of nuclear research is perceptibly slower than in the 1940s. Elements up to 104 or maybe 105 have been synthesized and there is talk that element 112 may have been produced (Marinov *et al.*, *Nature*, **229**, 464; 1971). In 1963 it was noted in studies of spontaneous fission of artificially synthesized elements that the average mass of the heaviest fragment remained constant at $A=142\pm 1$, while the mass of the light fragment increased when a range of nuclei from curium 248 (${}_{96}\text{Cm}^{248}$) to fermium 254 (${}_{100}\text{Fm}^{254}$) was considered (R. Brandt *et al.*, *Phys. Rev.*, **131**, 2617; 1963). If this trend were to continue a truly symmetric fission would not be obtained until the nuclear mass approached $A=284$. There has been speculation, however, that symmetry would be obtained at some lower mass where the characteristic strong binding energy associated with the nuclear magic numbers 50 and 82 manifests itself. Briefly, this arises from the fact that some nuclei with certain numbers of neutrons and protons are particularly stable. These are found experimentally to be 2, 8, 20, 28, 50, 82, and 126. A nucleus which has a magic number of neutrons and of protons, but not necessarily the same number, is termed doubly magic and is an even more energetically bound species. The values of the magic numbers are understood theoretically in terms of a neutron or proton moving in an average potential well formed by the other particles in the nucleus with the inclusion of a strong spin-orbit interaction. The resulting solution which gives the quantum levels of the particle in the potential well has well defined energy gaps at the magic numbers.

The fission fragments should therefore show some trend towards symmetry as the fissioning nucleus approaches ${}_{100}\text{Fm}^{264}$, which is composed of exactly two tin ${}_{50}\text{Sn}^{132}$ nuclei, a particular isotope of tin that has a doubly magic structure. Such a trend has now been reported by a group from Los Alamos (J. P. Balagna *et al.*, *Phys. Rev. Lett.*, **26**, 145; 1971). They have studied the spontaneous fission of ${}_{100}\text{Fm}^{257}$ and observe a much greater degree of mass symmetry than for ${}_{98}\text{Cf}^{252}$ and ${}_{98}\text{Cf}^{254}$ which they also studied.

The results from Los Alamos constitute the first piece of evidence for symmetric fission in this mass region. There is one fact, however, that makes the generalization of this result a dubious matter. The isotope ${}_{100}\text{Fm}^{257}$ has an

odd number of neutrons, so the properties of the fission are affected by the angular momentum and parity of the nucleus which is different from nuclei which have an even number of neutrons and protons.

The fission of one other nucleus with an odd number of particles has been studied in this mass region, einsteinium 253 (${}_{99}\text{Es}^{253}$), and the results obtained for this nucleus are consistent with those of its neighbours which have an even number of neutrons and protons. This, of course, does not imply that the fission of ${}_{100}\text{Fm}^{257}$ is characteristic of its neighbours. A much better test, as suggested by the Los Alamos group, would be to study the spontaneous fission of some other heavy nucleus such as ${}_{100}\text{Fm}^{256}$ or mendelevium 258 (${}_{101}\text{Md}^{258}$), or any heavier nucleus that may be available.

OCEAN FLOORS

More Nodules

from our Geomagnetism Correspondent

MANGANESE is not a particularly abundant element in the Earth, either within the crust or, if chondritic meteorites are any guide, within the deep interior. On average it forms only about 0.1 per cent of igneous rocks, compared with several per cent of iron; and because the manganese in oceanic sediments is ultimately derived from continental igneous rocks, concentrations there are not much different. All of which accounts for the great interest aroused by the discovery of manganese-rich nodules and slabs on the

ocean floor. A typical nodule contains between 6 and 24 per cent manganese, about the same concentration as iron. Clearly, such nodules cannot be derived from continents unless some remarkable concentration process has occurred. Their origin is not actually known, though because of a close association with volcanic rocks it is likely that the manganese-rich material was derived from lava as it extruded into the seawater.

Not surprisingly, manganese nodules and slabs have often been viewed in economic terms. But there is one snag. Most deposits lie at depths of 18,000–20,000 feet or more and far from land—a situation guaranteed to turn businessmen, economists and mineral prospectors off. But deposits newly discovered in the Kauai Channel, Hawaii, by Maury Morgenstein of the University of Hawaii are likely to make an altogether different economic story. For manganese nodules and crusts have been found at depths of only 5,000–8,000 feet and lying only 5–8 miles offshore. Moreover, they cover at least an area of 150 square miles to a thickness of over 10 inches in places. In short, Morgenstein has discovered an economically important reserve which is relatively easy to get at and which is likely to have a profound effect on Hawaii's economy in the longer term.

In fact, the story may not end there. It is possible, of course, that Morgenstein has by accident hit on the only manganese deposits in the area. On the other hand, in the vicinity of Hawaii there is a total of 3,750 square miles of shallow seafloor with the same geological conditions as the Kauai Channel, all within ten miles of land.

London Ash Revealed in Harwich

NATURE is full of mysteries; but few are so mysterious as those which science could in principle have solved at any time during the past hundred years or so but did not. Nobody would pretend that the minor mystery unearthed and solved by G. F. Elliott, of the British Museum (Natural History), and reported in next Monday's *Nature Physical Science*, is likely to change the face of geology. But all the same Elliott must have obtained a peculiar satisfaction from it; and for that he can be envied.

The problem which Elliott has solved is the relationship between the so-called London Clay of southern England and the similar deposits in continental Europe. The continental clay is marked by a thin ash layer near the base; but, in spite of the many petrological studies, no comparable layer has ever been discovered in England. As a result some geologists have suggested that the ash fall never in fact reached England and others have taken the view that the two clay deposits

were not at the same period of time.

It turns out that neither of these two assumptions are necessary. The London Clay which is exposed on the foreshore at Harwich contains a conspicuous stone band near its base. Indeed, this band has been known for more than two centuries, for in 1730 one Dale described it and noted that Harwich was paved with it. Elliott's studies now reveal that the missing ash is contained in this very stone band. Preliminary petrological examination of the ash suggests that it is very similar to that reported from the so-called London Clay in Denmark. It seems therefore that the English and continental ash layers are, after all, contemporaneous. The mystery is laid to rest. The English ash contains angular brown glass shards, some of which are streaky and resemble pumice, crystal fragments (often plagioclase) and lithic fragments full of opaque granules and containing minute, elongate feldspar crystals.

SELENOLOGY

Collapse Craters?

from our Geomagnetism Correspondent

LUNAR craters are, as every schoolboy knows, the result of meteoritic impact. But are all craters on the Moon impact craters? After all, the nature of the Apollo samples has been taken as evidence for the existence of lava flows on the Moon; and certain terrestrial lava flows contain craters of a different sort—volcanic collapse craters. Is it possible then that some lunar craters are caused by collapse rather than impact?

Terrestrial collapse craters are usually caused by deformation of partly cooled surfaces following withdrawal of fluid lava from beneath the crust during extrusion, or to drainage of surface material into subsurface cavities. If longitudinal structures such as fractures or lava tubes are present, the collapse craters produced are elongated and tend to form chains. If, on the other hand, there are no distorting structures the craters are circular and apparently distributed randomly. In other words, viewed from a distance they would probably be indistinguishable from impact craters. And so if there really are lava flows on the Moon it is reasonable to suppose that they, too, are liable to undergo collapse.

But short of close examination of the craters, how could such a hypothesis be tested? Greeley and Gault (*Science*, **171**, 477; 1971) have done it simply by comparing size-frequency distributions of lunar craters with those of known terrestrial collapse craters obtained under similar conditions. Thus, because the lunar counts were made from photographs of areas in and near Copernicus taken during Lunar Orbiter missions, terrestrial collapse craters in basalt at Modoc (California), Wapi Field (Idaho) and Laguna (New Mexico) were photographed at similar scales and under similar light conditions. The three terrestrial size-frequency distributions which resulted were similar and possessed two obvious characteristics—the maximum crater density is caused by craters in the range 8–12 m in diameter, and the slope of the cumulative crater density curve for craters of diameter greater than 10 m is about -3 .

The first thing to be said about the lunar size-frequency distributions is that most of them are quite different from those on Earth. Distributions from the continuous ejecta blanket, the flat dark fissured portion of the floor, the smooth inner wall and the smooth terraces on the rim flanks of Copernicus are similar to each other, but the cumulative crater density curve for each has a slope of about -2 . Distributions from the interior terraces ("flat, dark, smooth

often fissured terraces which appear to fill low regions between slump blocks of the inner crater wall") and a floor fissure flow ("a small, smooth, relatively uncratered unit associated with fissures on the floor") are quite different, however. They are, in fact, very similar to the terrestrial collapse crater distributions; and have, in particular, cumulative curve slopes of about -3 and a maximum number of craters in the range 11–16 m diameter.

The conclusion to be drawn from all this, according to Greeley and Gault, is that many of the craters on the interior

terraces and the floor fissure flow are collapse craters—a hypothesis put forward by Kuiper *et al.* some five years ago (*Calif. Inst. Tech. Jet Propul. Lab. Tech. Rep.*, 32–800; 1966). This could, of course, affect some indirect determinations of the age of the lunar surface. If lunar craters are caused by meteoritic impact, older surfaces will presumably have more craters than younger ones—a fact which can be used to assign relative ages to different parts of the lunar surface. But if a surface contains collapse craters in addition to impact craters, it will seem to be relatively too old.

Piecing Together the Life Stories of Meteorites

Two articles in Monday's *Nature Physical Science* may be signposts to the way in which a few of the holes in what is known about the immediate past history of meteorites will be filled in. The article by J. F. Lovering and his colleagues describes one of the few meteorites which has come near to doing anybody an injury—on the face of it meteorites have a surprisingly unimpeachable record considering that they are lobbed into the atmosphere at speeds of tens of kilometres per second. But on September 28, 1969, a meteorite fragment tore through the corrugated roof of a hay shed near Murchison, in Victoria, Australia, fortunately without striking anybody. The weight of meteorite fragments collected from the vicinity of Murchison after September 28, 1969, that have found their way into museums or the University of Melbourne adds up to 82.7 kg, but "a considerable quantity" is thought to have found its way into private hands, underlining the necessity for measures like that which has been laid before the British House of Lords to make all meteorites which fall in Great Britain crown property (see *Nature*, **229**, 446; 1971).

As well as giving a preliminary account of the Murchison meteorite, which seems to be a type II carbonaceous chondrite, the article by Lovering *et al.* raises the hope that an examination of the fragments will give details of how the parent body was shattered by the pulse of frictional heat as it struck the atmosphere. Apart from the intrinsic interest, the problem is significant because for determinations of meteorite age it is important to use fragments that have not been too much affected by heat. Most of the Murchison fragments have complete fusion crusts indicating that break-up took place while the meteorite was still moving fast enough to cause ablation. Some fragments have crusts of two thicknesses, the thicker presumably formed at an earlier stage in the fragmentation process.

In the second article knowledge of the effect of the heat pulse is carried a stage further by an examination of the Ucera

chondrite which fell in Venezuela on January 16, 1970. The intensity of the thermoluminescence from samples of meteorite depends on the heating that the samples received in the atmosphere, samples taken from near the fusion crust showing weaker thermoluminescence than deeper material. J. E. Vaz reports a systematic examination of the thermoluminescence along two axes through the Ucera meteorite, from which it is inferred that the temperature at 4 mm inside the final surface exceeded 120° C but did not reach 240° C, and that deeper than 1.5 cm the temperature cannot have been more than 120° C. This seems to confirm laboratory studies of the transformation in the metals and silicates of meteorites which also indicate a depth of penetration of the heat pulse a centimetre or so.

As well as showing that the thermoluminescence output has not been affected by the heat pulse other than in the outer 1.5 cm of the Ucera meteorite, the thermoluminescence measurements along one axis show a slight asymmetry about the centre. For parent bodies that were originally less than 2 m across, which would include the Ucera meteoroid, thermoluminescence is induced chiefly by cosmic radiation. Thus it rather looks as if the asymmetry in the thermoluminescence distribution means that the meteorite was shielded non-uniformly while it was exposed to cosmic rays in space. Non-uniformity of the heating in the atmosphere cannot be the answer because the meteorite is well rounded, and because of the similarity of the thermoluminescence output from samples adjacent to the fusion crust on different sides. A shielding effect is also indicated by the comparatively low ¹⁴C activity measured for the Ucera meteorite.

Oddly enough, for an old science that was under way in the last century, the study of meteorites is having a revival just now. Part of the story is a renewed interest in the determination of meteorite ages, but meteorites should also provide some kind of record of the past history of the cosmic ray flux.

Problems facing University Science

F. R. JEVONS

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Professor Jevons gives his own reflexions on a conference held in Manchester in January, and points to some of the changes that may have to be made in university science departments to cope with the problem that their size is likely to grow faster than their finances.

MORE teaching, less research, and universities becoming more like schools. That, roughly, is the prospect for the rest of the 1970s that emerged at a conference on problems facing university science organized by the Council for Scientific Policy (CSP) jointly with the Department of Liberal Studies in Science of Manchester University, and held in Manchester in January. Some rather drastic changes in academic science seem inevitable as Britain drags itself painfully into the era of mass higher education—with near-universal higher education on the Californian model as yet barely on the horizon.

Sir Frederick Dainton, chairman of the CSP, prophesied in his opening keynote address that there will have to be closer scrutiny of the real purposes of doing research, of the criteria for allocation of resources to research, and of the connexion between research and teaching. Already, he pointed out, something like £100 million a year is being spent on scientific research in British universities. There is little chance that this amount will grow anything like as fast as the 6 per cent a year increase in student numbers envisaged by the Department of Education and Science, and consequently most of the discussion at the conference was taken up with digesting various implications of the decrease in research intensiveness of the higher education system.

Disillusion

That such a change is inevitable was accepted almost without question. Recognition of public disillusion with science hung gloomily over the conference. It was not only Dr A. A. L. Challis of ICI who took the hardheaded business view that science does not lead easily and painlessly to increase in the gross national product. Other speakers also pointed to the widespread feeling of frustration over the promise of economic prosperity through science, accepted until not so many years ago with what now looks like simple minded faith. So often the modern marvels—the advanced power stations, the hovercraft—just do not work properly. Dainton listed some of the causes and symptoms which have turned the unclouded optimism of the 1950s into the present uncertainty: concern over the environment; the brain drain—now reversed, but more because of a changed situation in the United States than because of any improvement in Britain; the swing away from science in sixth forms; overspecialization at university and a shortage of candidates for traditional courses; unit costs rising in an atmosphere of tightening financial stringency.

When historians come to analyse the attitudes of the early 1970s, will they see all this breast-beating by the scientific community as early signs of a new realism or only as a swing of a pendulum? No doubt it is true that science has in the past been grossly oversold; only the naïve and the uninformed can seriously suppose that it can continue the

kind of growth it has enjoyed since the Second World War. But has the time perhaps come when more academics should jump off the self-denigratory bandwagon and recapture some of the old idealism? After all, together with the problems, science has delivered a lot of goods.

Future of Research Councils

One expression of the general feeling that society at large is not getting enough value out of investment in research appears in the rumours now current that some of the research councils might be taken over by the government departments corresponding to their chief interests. The idea would be to bring them closer to the users, so as to make their research strategies more user-oriented. In particular, the Agricultural Research Council is felt to be in danger of being taken over by the Ministry of Agriculture, Fisheries and Food, and Dr N. W. Pirie, of the Rothamsted Experimental Station, spoke of the unsettling effect on the scientists employed there.

As for the Medical Research Council, its secretary, Dr J. A. B. Gray, gave a spirited defence of the present system as against any possible marriage with the Department of Health and Social Security. His reasoning resembled the time honoured objection to monogamy: it was not so much a refusal to form one liaison as a reluctance to cut off all the others. The MRC, he pointed out, does not serve just one user but is the centre of a complex network of contacts, advice and support.

As chairman of the largest of the research councils—the Science Research Council—Sir Brian Flowers is in as good a position as anyone to give an inkling of what closer scrutiny over research funds might eventually mean in practice. The SRC's policy is to concentrate resources so that centres of excellence can be built up and maintained. Perhaps there are overtones of élitism in this approach, but the alternative is to spread resources so thinly that they cannot be effective anywhere. One implication of the policy of selectivity is that not all universities can be equally good at everything; perhaps only a dozen will become recognized as generally strong in science. Already the SRC is choosing fields of science for selective support. At present, however, 80 per cent of the funds for research grants is still being allocated by "passive response" to unsolicited requests, and only 20 per cent to "stimulated applications".

The case for concentration was reinforced by another line of argument put forward by John Ziman, professor of physics at Bristol University, who focused attention on graduate training rather than quality of research. Using order of magnitude calculations, he sought to show that the growth of higher education will so dilute the ratio of research students to university teachers that drastic selectivity will be unavoidable to maintain viable graduate schools in a limited number of centres.

What the crystal ball shows, then, is a hierarchy of institutions in which the differentiations are more, not less, marked than at present. Gone will be the polite pretence of equality of opportunity between universities. To most people it seems politically unacceptable to restrict entry to first degree courses because of assertions of the interdependence between teaching and research. But with how much equanimity can we move into a situation in which a high proportion of teachers for first degree courses will not be engaged on research? What will maintain the quality of their teaching? Will it be enough that once, years ago, they did

research? Can they be expected to keep in touch by in-service training and by rubbing shoulders with research workers?

The deeply rooted notion that the quality of teaching can be measured as an inverse function of its distance from the life-infusing light of research may have to be discarded. Belief in the dependence of teaching on research rests more on the frequency of repetition of the assertion than on solid evidence. There are those who point out that research can distract from teaching rather than enliven it. And it may be possible to find alternatives to research of the traditional kind. Engineers say that design and consulting work can also give the mind that liveliness which comes from being at a frontier of knowledge. Those who are oriented to teaching might even dare to suggest educational development work on curricula and teaching methods to act as research-surrogates in the occupational therapy prescribed by custom for academic staff.

Collaboration

"If you can't afford it, share it" was Flowers's prescription for high cost research. The alternative to opting out of expensive fields is to collaborate in them. It was a pity that there was so little discussion at the conference of the sharing of national resources between universities in Britain. A good deal of attention was, however, devoted to the more glamorous forms of collaboration that extend across national boundaries. The special favourite was, of course, the CERN accelerator at Geneva, on which papers were presented by both Dr A. W. Merrison, vice-chancellor of Bristol University, and Dr M. Gibbons of the Department of Liberal Studies in Science at Manchester. No one could have left the conference with any doubts still lingering about the immaculateness of its conception or the excellence of its execution.

There are, however, implications of this kind of research which still do not seem to be fully appreciated by much of the scientific community. In high energy nuclear physics, even the most academic of scientists cannot be free to do experiments "just to see". He accepts, without too much grumbling, that his proposal has to run the gauntlet of a series of committees. It may take three years, if all goes well, to get an allocation of beam time on the big machine. The organization of an experimental run reminded Gibbons "of a production process in industry or the NASA mission control centre at Houston". So what has become of the traditional idea that good research is possible only when the intellect is left free to explore ideas unhindered? In Britain, the national research effort has to be oriented to the international programme. Universities must be willing to release staff to work at the big machine—but this means that links between the research and the educational system become increasingly tenuous.

Problem-orientation

No conference such as this could have gone by without criticizing university courses for being overspecialized. Dr T. M. Sugden, of Shell's Thornton Research Centre, complained that first degree graduates commonly have indigestion and PhDs are liable to suffer from constipation. Varying the metaphor, Sir Robert Cockburn, formerly director of the Royal Aircraft Establishment, Farnborough, judged that it takes an average of three years to "defrost" a university graduate.

The fashionable remedy—laxative or anti-freeze as the case may be—is to swing from discipline-orientation to problem-orientation. Clothed in various vocabularies and contexts, this was a recurrent theme. Professor A. H. Bunting, of Reading University, stressed the "primacy of the problem", with science put in its place as just one of the resources for achieving solutions; from his own field, agriculture, he illustrated this by the marked success of a highly

mission-oriented US team in increasing food production in India more in four years than the British did over a much longer time.

Alan Pearson, director of the Research and Development Research Unit of the Manchester Business School, gave a specification of the abilities required of scientists working in industrial environments: to identify problem areas, to handle unstructured problems, to work effectively with other people, and to communicate with non-specialists. But can such qualities be taught? Only, he thought, through project-based courses, the projects preferably being set up jointly with industry, in spite of the expense and difficulty involved. This approach clearly cannot be envisaged for all undergraduates—it could be adopted only on a more select basis, chiefly at postgraduate level.

Listening to criticisms of university science, one begins to feel that it has all turned into a sort of ritual: the practical problem is the totem, specialization is taboo. This is not to say that such criticism is no longer necessary. But perhaps it should now be directed less at the universities, which have already innovated more than many people recognize, than at those schools which continue to send most of their ablest sixth formers to the more traditional courses, ignoring or distrusting the new.

The difficulty with new courses, of course, lies in distinguishing the hasty pot-pourri from the carefully planned and well served meal—it must be admitted that change is not always progress. Courses that look too much outward at real life problems can give the appearance of a Certificate of Secondary Education philosophy extended, far beyond the one extra year provisionally blessed last summer by the Schools Council, into the less appropriate realm of the universities. Academics tend, whether rightly or wrongly, not to recognize such work as suitable preparation for more advanced study, so projects develop into educationally terminal diseases.

Moreover, there are limits to what can be expected from an educational system. Some critics seem to imply that universities are failing to help young people achieve their ambition to do well in industry. The fact is that many of them have no such ambition. Imbued with vague anti-materialist sentiments, they often fail to crystallize these sentiments into any specific activity, such as teaching in an underdeveloped country, and this is what so exasperates the careers adviser. But can a university teach students to want money more urgently? And if it could, should it?

More Open Politics ?

An intriguing aspect of the conference was the sprinkling of younger scientists mixing with the "establishment" men; not that they made much impact, outnumbered as they were. Most of the talking was done by "that self-congratulatory group who have got out of the system all they want", as Flowers put it. Nevertheless, there was a feeling that a conference such as this could not have happened even a few years ago. The politics of British science has hitherto been a very closed affair. However rosy the SRC might be described as "a forum of the scientific community", to most practising scientists it has seemed, like all the science policy bodies, more like an outpost of inscrutable officialdom. Are the policy makers now moving to more open, more "democratic" decision-taking, so as to counter accusations that they are a faceless gerontocracy of committee men meeting behind closed doors?

If so, they could have a long way to go. They might have to do more than include a few lecturers among the professors on the carefully constructed invitation lists. Can we envisage faculties sending elected representatives of non-professorial staff to future meetings? Or even students? It seems an unlikely prospect. With policy so firmly set to sacrifice equality to quality, it is hard to imagine the political structure moving far in the opposite direction.

Defence of the Berkeley Work on Alpha-emitting Isotopes of Element 104

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In the past two years, there has been some controversy about conflicting claims of Russian and American scientists to have demonstrated the formation of isotopes of Element 104 by nuclear reactions induced by high energy particles. This article is a restatement of the American case by Professor A. Ghiorso's group at Berkeley.

CERTAIN questions have been raised regarding the validity of our work¹ on the discovery of two alpha-emitting isotopes of element 104 (rutherfordium). Doubt was first expressed by V. A. Drulin at the international conference on nuclear reactions induced by heavy ions² at Heidelberg, Germany, in July 1969. These doubts were repeated in a paper submitted to *Yadernaya Fizika*³ in November 1969 by Akapiev *et al.* In this same month the Robert A. Welch Foundation Conference on Transuranium Elements—the Mendelev Centennial was held at Houston, Texas, and the issues were discussed at length after the presentation of papers⁴ by A. Ghiorso and by I. Zvara. Apparently this discussion did not sufficiently clarify the matter because strong doubts were again published in *Atomnaya Energiya* by G. N. Flerov⁵.

In our article⁶ on the discovery of an alpha-emitting isotope of element 105 (hahnium), we carefully included answers to the major criticisms, but in view of the continued charges made by the Dubna group we feel that a detailed rebuttal is in order. We shall attempt here to perform this function and in addition will present new evidence in support of our original work.

The research on the heavy element alpha-emitters is fraught with the hazards of low production cross sections which lead to numerous possibilities of misidentifications because of the presence of background activities with similar alpha energies and half-lives. Having pioneered in this field we are aware of these problems and have devoted much of our efforts to determining and eradicating sources of troubles. We feel that we have been conservative in our published claims and are thus much surprised by some of the criticisms levelled at our work. Perhaps we have misjudged the necessity of including a very detailed discussion of possible background effects.

A review of the general methods used in these experiments will help to clarify the discussion of our results. The basic technique takes advantage of the large forward recoil imparted in a heavy ion reaction to separate the transmuted atoms from the usually highly radioactive target. In order to provide a very thin sample for alpha particle energy

analysis, the recoiling atoms are stopped in helium gas at a pressure of 500–1,000 torr and then allowed to escape with the gas through a small orifice into a rough vacuum where they impinge and stick on the rim of a 50 cm diameter wheel. The wheel acts as a conveyor and periodically carries these deposited atoms to positions adjacent to solid state silicon alpha detectors for energy analysis. Half-life information is obtained from the relative numbers of alpha particles observed at each detecting station and also from the decay observed at each station while the wheel is stationary. The data are stored by a PDP-9 computer and ancillary equipment.

In favourable cases, it is possible to determine the mass and atomic number of the nuclide being studied by identifying the daughter nucleus which recoils from the rim of the wheel as the result of alpha particle decay of its mother. To make this measurement possible, the detectors which have been adjacent to the wheel are shuttled about 2 cm to positions opposite similar detectors at suitable intervals so that they can be examined at high geometry for the daughter activity. In our first published experiments on element 104, we used four mother and four corresponding daughter detectors. Later, to recover the time lost while the mother detectors were shuttled off the wheel, the detector system was duplicated so that the mother and daughter measurements could be made simultaneously. Thus, at each station four detectors were installed, two shuttled and two unshuttled. The number of detecting stations was first increased to five and finally to seven so that our present system makes use of $7 \times 4 = 28$ detecting crystals (Fig. 1).

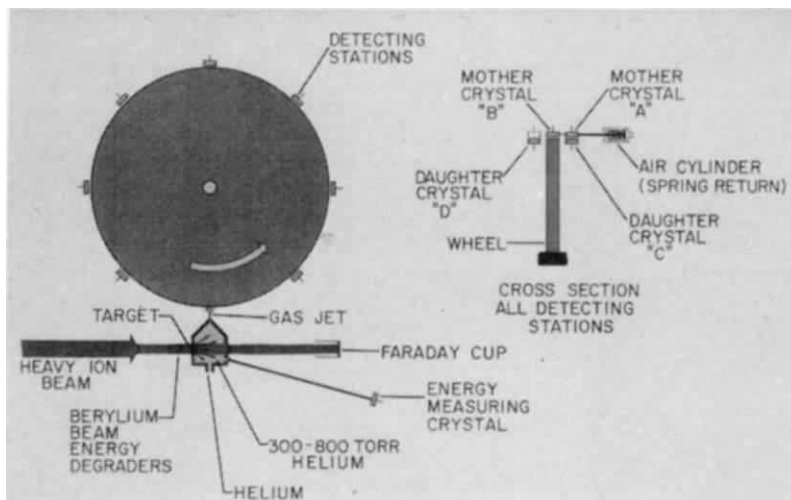
We now take up the criticisms raised by Akapiev *et al.*³. We will first present what we believe to be a fair statement of the major charges raised by that report and then follow it with our answer. To help the reader follow the arguments, we have reproduced two figures (Figs. 2 and 3) along with their captions from the original publication.

The Berkeley group did not present alpha spectra of background activities that would be produced by the bombardment of lead impurities with carbon ions and did not discuss any background effects

These statements are both true. Because of the stringent word and figure limitations set by *Physical Review Letters*, there was no detailed discussion of this aspect of the experiments. We did, however, carefully state that we had made bombardments with other ions and thus implied that suitable background checks had been made. The fact that certain Pb-produced peaks in the alpha spectra such as ²¹⁴Ra and ²⁰⁹, ²¹⁰, ²¹²Rn were labelled also implies that we were clearly aware of background effects caused by a lead impurity. The simple fact is that the element 104 alpha activities were so clearly above the backgrounds usually encountered that this problem was almost irrelevant. Thus we devoted the space available to other important phases of the experiment.

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Fig. 1 A schematic representation of the vertical wheel system with seven detecting stations. On the right hand side a cross-section of one of the detector stations is shown.



Well known Pb-produced nuclides do not decay with their proper half-lives, e.g., 30 min ^{209}Rn and 2.7 h ^{210}Rn

The main activity in the 6.043 MeV labelled peak is due to ^{210}Rn and arises as the alpha-recoil daughter of 2.6 s ^{214}Ra which is produced from a tiny lead impurity in our californium target. Since the Rn isotopes will not stick to the wheel as they emerge from the gas jet (this can only happen if the collecting surface is cooled to a very low temperature), they can only appear in the spectra either by being detected as gaseous atoms in the wheel housing or by being embedded into the detector surfaces by nuclear recoil. As we shall show, the former condition does not prevail. But in the latter case, the Rn isotopes would appear to have the half-life of the mother atoms since the amount deposited into each detector face would depend on the wheel-cycle period. If the half-life is measured by the relative amounts of activity seen by each detector, the mother half-life would determine its value, but if the decay at each detector is monitored, the half-life of the daughter would be measured. Thus it was that the 6.043 MeV peak appeared to decay in the successive alpha spectra with a 2.6 s half-life since it was controlled by ^{214}Ra . There must have been some ^{209}Rn (which has the same alpha energy) present in this peak since it is produced as the daughter of 2.75 min ^{213}Ra , but it was a minor component.

The alpha particle peak at 8.87 MeV can only be due to the 25 s ^{211}mPo and thus cannot decay with a 3 s period

We were very careful to point out that the origin of the 8.87 MeV peak was uncertain and we did not claim that it was due to $^{257}\text{104}$. From recent results, we find that several sources can contribute to this peak in the alpha spectra.

(a) One obvious source, it is true, is 25 s ^{211}mPo , as demonstrated in Fig. 5, where a lead target with some 50,000 ng cm^{-2} has been substituted for the ^{249}Cf target which contains about ng cm^{-2} Pb impurity. The polonium activity has a 25 s half-life both as measured from the relative amounts of activity observed at each station and by the decay while the crystals are stationary.

(b) When our work¹ was published, we were unable to assign the short lived component in the 8.87 MeV peak to any known nucleus, as was pointed out in the figure caption (Fig. 2). Not until we started working on element 105 did we accumulate conclusive evidence that ^{257}Lr has a half-life of 0.7 s and also a most prominent alpha group at 8.87 MeV, as opposed to the Dubna group's⁷ claim that it has a half-life of 35 s and an alpha energy of 8.5–8.6 MeV. By resolving the 8.87 MeV peak of the repeat experiment (to be discussed later) into two components we find that about one half of the activity is due to 0.7 s ^{257}Lr and the other half to 25 s ^{211}mPo .

(c) It is conceivable that 5 s $^{257}\text{104}$ can have a weak alpha group at this energy but this cannot be resolved easily because of the interfering activities.

All Berkeley half-lives in the heavy element region must be questioned because the apparent half-life of 30 min 7.43 MeV ^{250}Fm is obviously only a few seconds

For some time, the strange phenomenon associated with the peak at 7.43 MeV troubled us greatly. We at first quite naturally assumed that the apparent short half-life of about 2 s was a real measure of the half-life of this peak and so thought it might be due to 0.5 s ^{211}Po , which has this energy, plus some longer lived background. We finally discovered

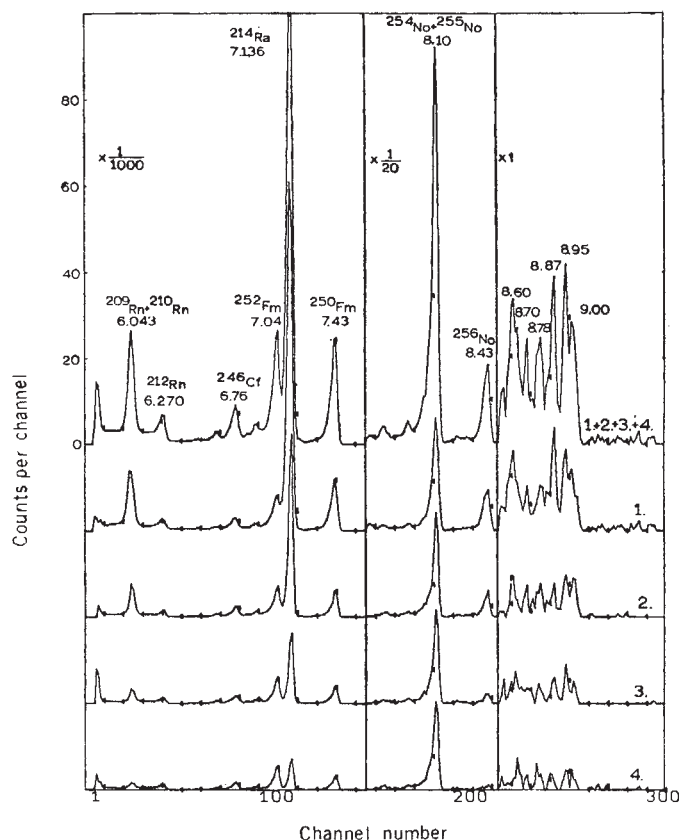


Fig. 2 "A series of alpha spectra of the activities produced by bombardment of ^{249}Cf with 71 MeV ^{12}C ions. The top spectrum is the sum of the individual spectra from the four detectors. The 8.60 MeV peak is probably due to ^{258}Lr ; the peaks above that energy belong to $^{257}\text{104}$ with the exception of the one at 8.87 MeV whose origin is uncertain¹". (See text: this peak is now known to be due to ^{257}Lr and ^{211}mPo .)

that the peak persisted after bombardment ended and decayed with a 30 min half-life at each detector even when the wheel was removed. Further, it was found that the ^{246}Cf daughter of ^{250}Fm was also observed in each crystal and corresponded roughly to the amount of its parent. It was obvious then that the activity was ^{250}Fm which had been transferred to the face of each crystal, and the question became that of knowing how the atoms lodged there. They could not have been transferred as the result of alpha recoil from ^{254}No for two reasons: first, the number of atoms required was far in excess of that observed and, second, half-life is well known to be $55 \text{ s}^{8,9}$.

Over a period of time we have made additional observations and experiments so that now we can offer the following explanation which appears reasonable. We have found that another isotope of fermium, ^{258}Fm , which was made in good yield at the same time as ^{250}Fm , was not transferred. We also found that ^{254}No was transferred to the detectors with a 0.2 s apparent half-life, even though another isotope of nobelium, ^{255}No , was not. We also looked with high sensitivity but without success for the transfer of the prominent activities ^{214}Ra and ^{213}Fr . We decided that the movement of atoms from wheel to detector was not a mechanical or chemical effect but must be due to the recoil afforded by transitions from isomeric states in the two nuclides, ^{250}Fm and ^{254}No . To prove that this was the case, we biased the wheel negatively by 10 V relative to the crystals and in-

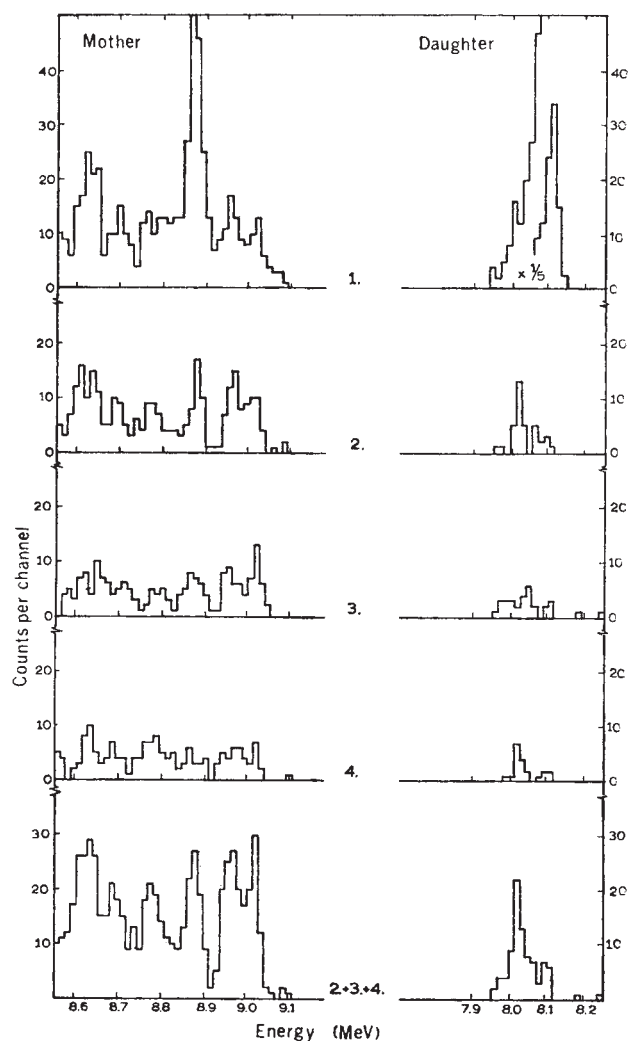


Fig. 3 "A set of spectra from the mother-daughter experiment which demonstrates the genetic relationship between $^{257}\text{104}$ and ^{253}No . The spectra recorded by the individual crystal pairs are shown on top with the sum of the last three pairs at the bottom"

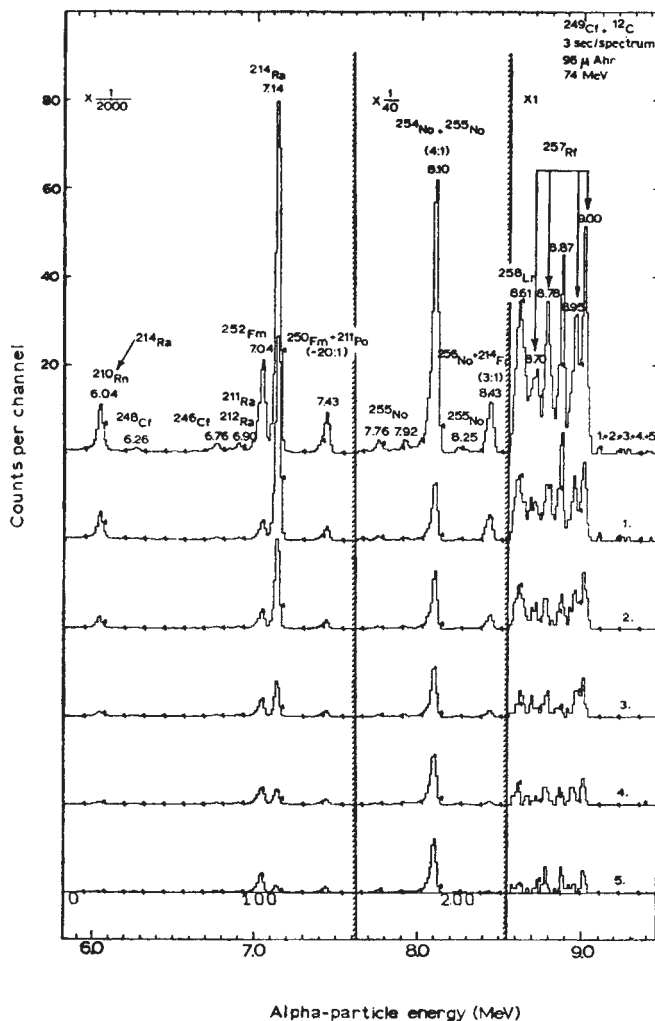


Fig. 4 A series of alpha particle spectra of the activities produced in repeat experiments when bombarding the ^{249}Cf target with 74 MeV ^{12}C ions. A 20 detector system was used instead of the 8 detector one used in the experiments resulting in the spectra shown in Fig. 2. The wheel cycle rate was 3 s in both series of experiments.

creased the gas pressure in this region to 5–10 torr. By this technique we were able to reduce the transfer of these activities by an order of magnitude.

A very strong corroboration was furnished by the bombardment of ^{249}Pu by ^{12}C ions. At 72 MeV, which is near the peak of the ($^{12}\text{C}, 4n$) reaction, the transfer of 30 min ^{250}Fm was observed with the same apparent half-life as in the carbon ion bombardment of ^{249}Cf . This experiment rules out the rather remote possibility that a 2 s ^{250}Md , decaying by electron-capture, can be the source of the transfer of ^{250}Fm since elements with atomic number greater than 100 cannot be made in this bombardment. It is also extremely unlikely that a 2 s beta-decaying isomer of ^{250}Es can be responsible. We can only conclude that an isomer exists in ^{250}Fm itself and a final test which is to be conducted will be with the reaction $^{249}\text{Cf}(\text{He}^4, 3n)^{250}\text{Fm}$. A full report on this very interesting nuclide will be published later.

With only the evidence afforded by this unusual transfer phenomenon, the Dubna group suggested that all of our half-life measurements could be in error because of some undiscovered artefact of our system. Suffice it to say that we have obtained the same values for many nuclides as they have and most of these half-lives were measured before their published work. These measurements vary in range from 3.2 s⁹ for ²⁵⁶No (which from 1963 to 1967 was quoted as 8 s by its Russian discoverers¹⁰) to 200 s¹¹ for ²⁵⁵No.

Apart from statistical considerations, we have found no reason to doubt our decay periods.

The construction and geometry of our set-up cause "3 s" to be a characteristic value in our measurements. In particular, activity may be collected directly on the detector faces by gas-jet leakage around the wheel

To determine whether a small amount of activity could bypass the wheel and be collected on the detector faces, we have performed an experiment to measure such an effect. In our normal conditions, some 2×10^6 alpha counts of ^{214}Ra were observed from carbon ion bombardment of a lead target with the wheel being cycled at a rate of 3 s per detecting station. The wheel was then stopped and the measurement repeated for an identical integrated beam charge. Not one count which could be ascribed to ^{214}Ra was observed in any of the detectors. This was not particularly surprising to us since the volume through which the wheel is rotated is carefully shielded internally by lead sheets to reduce the fast-neutron degradation damage of the silicone detectors. We feel we can state categorically that in our system there is no significant direct transfer by a gas leakage path. Our "3 s half-lives" can only be the result of nuclear characteristics beyond our control.

The half-lives of $^{257}\text{104}$ and $^{259}\text{104}$ could be much shorter because there is an excess of ^{253}No and ^{255}No on the first detector

This criticism must be answered in two ways. (a) If there were such an excess of these two isotopes on the first detector, then why would not the alpha particles from their presumed parents be also observed in this same detector? (b) We never said that there was an excess of either ^{253}No or ^{255}No in the first detector. The excess activity was identified as ^{254}No (from its decay on the detector with a 55 ± 20 s half-life). We used this isotope of nobelium as a monitor of the amount of "self-transfer" in the daughter measuring experiment. It now seems that this transfer was accomplished by the decay of the ^{254}mNo I.T. with a 0.2 s half-life as we have explained.

The Berkeley experiment can be compared with a background run made at Dubna with a lead plus carbon ion bombardment which shows an overwhelming ratio of ^{211}mPo to ^{214}Ra

The Russian experiment is by no means a suitable substitute for our experiments on element 104. They used a lead target weighing $1,500 \mu\text{g cm}^{-2}$; we used a californium oxide target weighing about $300 \mu\text{g cm}^{-2}$. They used a mixture of helium and nitrogen gases in their recoil chamber; we used only helium. The recoil chamber dimensions and gas pressure are not given but we suspect that they must be using one much larger than ours at a higher pressure and thus capable of stopping more noncompound-nucleus recoils. It has been our experience that the yield of ^{211}mPo depends critically on these parameters and on other factors such as the impurity content of the carrier gas—even beam level can play an important role. Our experiment has been carefully tailored to maximize the heavy nuclide yield and reduce that of interfering activities, and so it should not be too surprising if our ratio of ^{211}mPo to ^{214}Ra is lower than in their experiment. We do know that there is some ^{211}mPo in the 8.87 MeV peak, but it has not affected the interpretation of the nearby alpha groups which belong to $^{257}\text{104}$. It is clear that the Dubna system operates differently from ours because of the large amount of ^{213}Rn (8.09 MeV peak) visible in their spectrum. It seems to us that this can be observed only by decay from gaseous atoms of radon in the vicinity of the detectors since the amount is hundreds of times larger than that which could come via electron-capture branching

from the 6.77 MeV ^{213}Fr , no trace of which is visible in the Russian spectrum.

These criticisms and their rebuttals we believe to be a fair summary of the arguments levelled at our experiments. A more satisfying answer, perhaps, is furnished by what follows. We have repeated the $^{249}\text{Cf}(^{12}\text{C}, 4n)^{257}\text{104} \rightarrow ^{253}\text{No}$ experiment with a higher efficiency and better resolution. A background experiment was also performed with a $50 \mu\text{g cm}^{-2}$ lead target. This was not exactly a substitute for the californium experiment, serving only as a reasonable approximation, but it did show that ^{211}mPo was not an important problem. The new experiment on element 104 gave statistically better information than the previous run even though it was completed in a shorter time.

The results of the repeat experiments are presented in Figs. 4, 5 and 6. The first one displays a series of alpha particle spectra of the activities produced in bombardments of the ^{249}Cf target with 74 MeV ^{12}C ions. The experiment was carried out with the 20-detector system and the spectra shown are from the detectors in the on-wheel position. The wheel-cycle rate was 3 s per detecting station. The activities assigned to isotopes of Ra, Fr, Rn and Po are due to a lead impurity in the target. A small amount of mercury contaminant in the material backing the target does not significantly add to these activities. Where two activities contribute to the same peak, the approximate ratio of the two is shown below the peak label. It should be noted that the 6.26 MeV peak is predominantly due to ^{248}Cf , not ^{212}Rn (Fig. 2). The 6.04 MeV ^{210}Rn peak has the apparent half-life of its mother, ^{214}Ra , because the observed events are mostly due to the decay of ^{210}Rn atoms recoiled into the detectors as a result of the alpha decay of ^{214}Ra atoms.

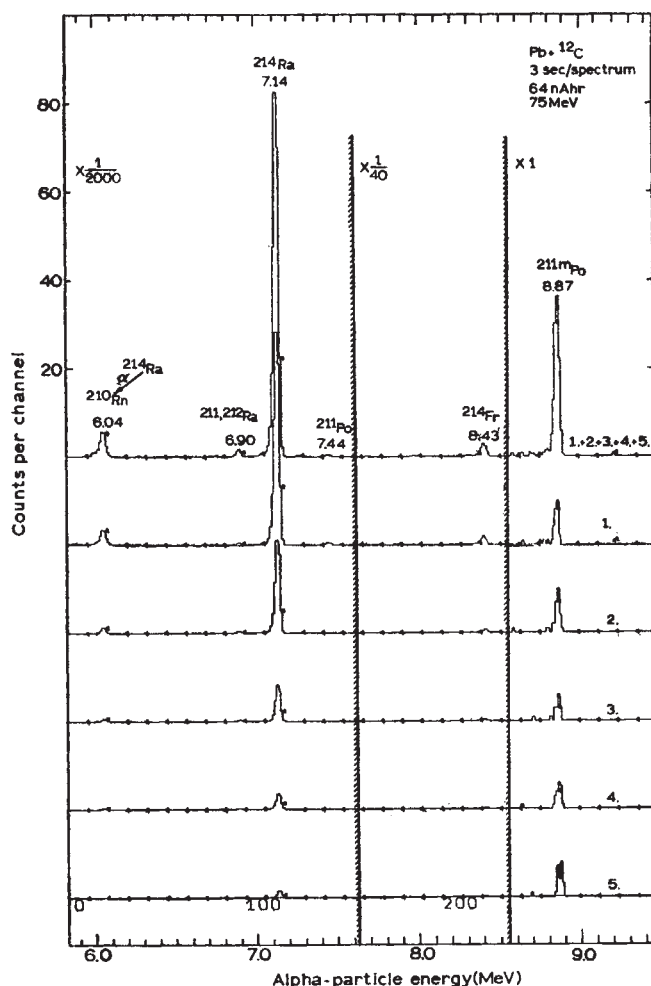


Fig. 5 Alpha particle spectra resulting from an experiment where the ^{249}Cf target was replaced by a lead target.

The peak at 8.87 MeV results from the decay of ^{257}Lr and $^{211\text{m}}\text{Po}$, both of which contribute about equal amounts. The assignments of the 0.7 s component to ^{257}Lr was confirmed in connexion with the experiments on element 105 by a cross-bombardment utilizing the $^{249}\text{Cf}(\text{B}^{11},\text{n})^{257}\text{Lr}$ reaction.

Fig. 5 displays a series of alpha particle spectra of the activities produced in bombardment of a natural lead target by ^{12}C ions under similar conditions to those in Fig. 4. The ratio of $^{210}\text{Rn}/^{214}\text{Ra}$ is smaller than in Fig. 4 because the decay of ^{210}Rn was not followed equally long after the bombardment. Because of the differences in target thicknesses and beam intensities, and the difference of about 1.5 MeV in the bombarding energy of the ^{12}C ions, the ratio of $^{211\text{m}}\text{Po}(8.87\text{ MeV})/^{214}\text{Ra}(7.14\text{ MeV})$ is greater by a factor of two in the lead spectrum.

The series of alpha spectra from the same experiment as in Fig. 4, but recorded by the crystals in the off-wheel position, is shown in Fig. 6. The on-wheel-off-wheel cycle, or shuttle period, was 100 s, while the wheel-cycle rate was 3 s. The presence of ^{250}Fm and ^{254}No alpha particle peaks with apparent half-lives of 2 s and 0.2 s, respectively, is believed to be caused by isomeric states of these isotopes, as previously explained. The other peaks in the spectrum are caused by the decay of alpha-recoil atoms on the movable detectors.

The apparent half-life of ^{253}No obtained by measuring the amount of ^{253}No recoiling at each detector station is 4.4 ± 1.0 s. This is in agreement with the value 4.8 ± 0.5 s for $^{257}\text{104}$ as measured directly by the amount of activity observed at each

station. Summing the detected daughter events by the four 25 s time subgroups of the 100 s shuttle period, one obtains a half-life of 90 ± 30 s for the 8.01 MeV alpha particle group which is consistent with the 105 s half-life⁹ of ^{253}No . The ratio of counts in the alpha particle peaks assigned to $^{257}\text{104}$ to those in the 8.01 MeV peak in Fig. 6 is 506:137 or 3.5. A calculation taking into account geometry and timing conditions gives a value 2.5. This difference could possibly be an indication of some 20–30% electron capture branching in the decay of ^{253}No .

The same equipment has been used to discover another isotope of rutherfordium. This work¹² characterized the 65 s alpha emitter, ^{261}Rf , and showed conclusively that its 26 s daughter, ^{257}No , was observed as the result of alpha particle recoil-transfer from its mother. This discovery was confirmed chemically when it was shown¹³ by fast aqueous chemistry experiments utilizing this isotope that rutherfordium was a trans-actinide element. More recently, this system has been used in the discovery⁶ of an alpha-emitting isotope of element 105, the 1.6 s ^{260}Ha . The fact that the radiations detected in these two sets of experiments were completely different shows that there is no built-in constant background effect that could conceivably mislead us in our interpretations of other results.

In conclusion, we feel that we can safely draw the following conclusions: (1) The additional experiments with ^{257}Rf which have been described above fully confirm our original findings. (2) The puzzling transfer phenomenon has been explained as the result of previously unknown isomeric transitions in the even-even nuclides, ^{250}Fm and ^{254}No . (3) The unknown 0.7 s and 8.87 MeV activity has been determined to be due to ^{257}Lr . (4) There is no gas leakage in our system that can transfer activity directly to the detector faces. (5) Our system does not have a "characteristic half-life due to some unexplained artefact".

In our opinion the performance and reliability of our experimental system are beyond reproach. The present multi-detector shuttle apparatus is quite a complicated instrument which has required a great deal of development and testing, and its value as a research tool has been proved by the quality of the nuclear spectroscopic data obtained for the seven isotopes of nobelium, five of lawrencium, three of rutherfordium, and one of hahnium which have been characterized up to the present time.

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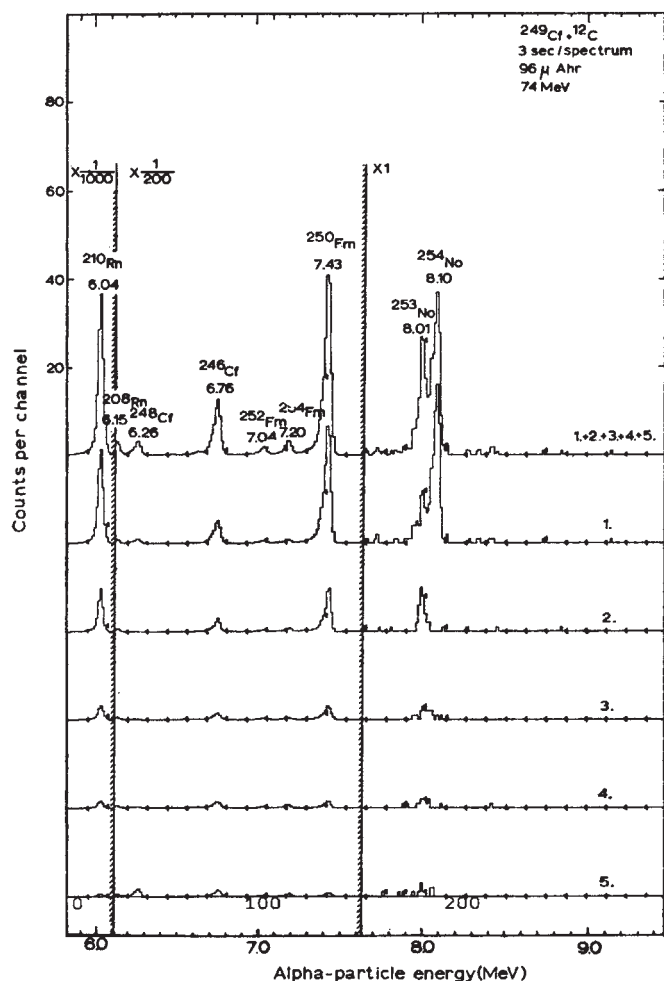


Fig. 6 A series of alpha particle spectra from the same experiments as in Fig. 4 but recorded by the crystals in off-wheel position. These spectra correspond to those displayed in Fig. 3, but show a wider range of alpha particle energies.

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Ageing of Mammals

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In his theory of ageing Professor Bullough suggests that in mammals it is stress which delays cell death through its effect on the chalone mechanism.

THE phenomenon of ageing and death presents a biological problem of the greatest interest and importance¹⁻⁴. The most basic question is whether ageing is an inherent feature of all cells and organisms. If it is, then a long life must be regarded as the mere postponement of inevitable death; if it is not, then a limited life span must be something which has been superimposed, presumably because it confers some benefit on the species. It seems that this second alternative is to be preferred, and indeed Weismann⁵, in 1891, concluded that death, wherever it is found, "can be very well explained as a secondarily acquired adaptation". Certainly most protozoans or many lower metazoans "fail to show ageing . . . because of a continual replacement regimen" and so they have an "indeterminate" life span⁶.

According to Comfort⁶, senescence depends essentially on "a cellular information loss, probably in fixed cells, and originally at the molecular level". The theories on information loss fall into two groups, which are not necessarily exclusive. The first holds that ageing is due to the steady accumulation of random and permanent forms of cell damage leading to reduced function or to malfunction in one or more vital tissues. The second holds that ageing is basically directed by some inbuilt control mechanism. According to Medawar⁷ and Williams⁸ this mechanism may depend on the actions of "pleiotropic genes", which are advantageous in a young animal at the expense of their becoming disadvantageous later in life. However, such genes remain hypothetical, and Sacher⁹ has trenchantly concluded that although "physically possible" they are "absurdly unlikely".

A more tenable viewpoint emphasizes the potential importance of a mechanism of ageing which is not hypothetical and which is controlled by genes that continue to act in the same way throughout life⁴. This mechanism, which is basic to tissue organization, is already known to determine the life span of cells of many mammalian tissues, and at least in theory it could readily be adapted to determine the life span of the animal itself. It is this theory that is examined here.

Tissue Organization: Cell Gain

The key to the mortality of mammals certainly lies in their tissues, which although superficially diverse are all organized to the same plan. Each tissue and each organ must be maintained at a mass which is appropriate to the total body mass; this is a problem of cellular homeostasis.

Cellular homeostasis is based on mitotic control. In theory it is possible to envisage the creation of an animal by mitosis and differentiation and then the survival of that animal through an adult life in which no further mitosis or differentiation occurs. Such a situation may exist in many adult insects and it is certainly found in the non-mitotic neural and muscular tissues of mammals. However, most mammalian tissues retain a mitotic potential which is invaluable for the repair of damage.

In all tissues examined so far the method of mitotic control is essentially the same: the rate of production of new cells is determined from moment to moment by a negative feedback system⁴. The tissues already studied from this point of view are epidermis¹⁰, sebaceous glands¹¹, melanocytes¹², lung alveoli¹³, kidney^{14,15}, liver¹⁴, granulocytes¹⁶, erythrocytes¹⁶, and lymphocytes (unpublished results of E. B. Laurence and myself); in all these cases the cells synthesize a tissue-specific antimitotic messenger molecule, called a chalone, which limits the rate of cell production (Fig. 1, point A). Chalone control systems may be present in all mammalian tissues, although in some tissues other control systems, which are commonly hormonal, may be superimposed⁴.

Of particular interest has been the discovery that the anti-mitotic power of most of the known chalones is strengthened by the presence of the two stress hormones (adrenaline and a glucocorticoid hormone). It is this which gives rise to the well known diurnal mitotic cycle¹⁷: with low stress hormone output during sleep the mitotic rate rises and with increased stress hormone output on waking the mitotic rate falls. This mechanism may have little practical significance in normal circumstances but in the wild it may act in stressful situations, especially during long periods of hunger, to reduce the metabolic demand of an unnecessarily high rate of cell production.

All mitotic tissues contain two basic cell types: those which are involved in the mitotic cycle and those which are post-mitotic and which are passing along the ageing pathway to their death (Fig. 1). Thus each tissue is in a state of flow and it is the post-mitotic ageing cells that are responsible for tissue function.

Any cell entering the ageing pathway has a particular life expectancy that is typical of that tissue. It is well known that the higher the mitotic rate the shorter this life expectancy: in epidermis with a moderate mitotic rate the post-mitotic life span is 14-21 days^{18,19}, while in duodenal mucosa with a high mitotic rate the life span is only about 2 days⁴. These tissue characteristics, however, are not inflexible. If in any tissue the mitotic rate increases, so too does the rate of ageing of the post-mitotic cells; thus in epidermis with chronic irritation or psoriasis the life span of the post-mitotic cells is reduced to 4-5 days^{18,19}. Conversely if the mitotic rate falls, as in epidermis and sebaceous glands during continued stress, the rate of post-mitotic cell ageing is also reduced²⁰. These changes in the cellular life span ensure that the tissue neither becomes too gross (perhaps even to the point of tumour formation) nor shrinks to the point at which the life of the organism is endangered.

They also show clearly that a post-mitotic cell does not normally die because it is worn out but that its time of death is dictated, according to circumstances of the moment, by the same physiological mechanism that controls the mitotic rate.

In a mammal the neurones and the skeletal and cardiac muscles are established by mitosis early in life, especially during the embryonic and foetal stages. At some time shortly after birth the mitotic genes are switched off and thereafter growth in tissue mass is achieved by growth in cell size. By the same means the adult skeletal and cardiac muscles can temporarily increase in mass to meet a temporary increase in metabolic demand, and a similar response is also possible in the cells of some mitotic tissues.

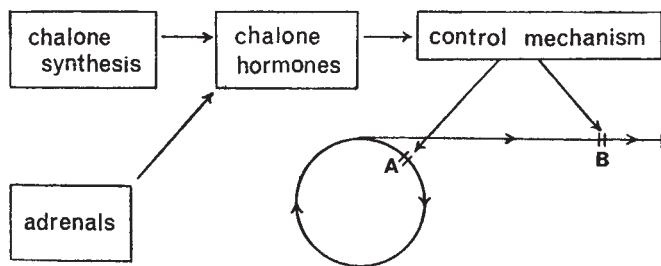


Fig. 1 Diagram of the chalone control mechanism in a typical mitotic tissue such as epidermis. Chalone action is strengthened in the presence of the two stress hormones from the adrenals. An inhibition of mitosis at point A is accompanied by an inhibition of cell ageing at point B.

The situation in a typical non-mitotic tissue is shown in Fig. 2 (compare Fig. 1). Although the mitotic genes are inactivated, the other half of the normal pattern of tissue organization, the ageing pathway, is apparently still functioning. It has already been noted that a reduction in mitotic activity is accompanied by a prolongation of the ageing pathway, and it is obviously to be expected that in non-mitotic tissues this pathway will be particularly long. This is certainly true in neurones and in the skeletal and cardiac muscles, but although the inhibition (Fig. 2, point B) preventing cell death is powerful, it seems that it may not be absolute and that the loss of cells may continue throughout adult life²¹. It has been suggested that in the adult human brain some 10,000 neurones pass this point to die every day²², and even if this figure is grossly inaccurate the principle evidently holds. In an old mammal the reduction in brain size, as well as in skeletal and cardiac muscle mass, seems obvious, but much further study is needed especially since contrary evidence has been published²³.

Ageing of Organisms

The search for the basic mechanism which ensures the mortality of the mammals has involved both the mitotic and the non-mitotic tissues.

Regarding the mitotic tissues the most important evidence comes from Hayflick²⁴, who has found from experiments *in vitro* that while fibroblasts from human embryonic lungs are capable of fifty to sixty doublings, those from adult lungs are only capable of twenty to twenty-five doublings. He has consequently concluded that the cells of mitotic tissues have only a limited mitotic potential and that this may be an important factor limiting the life span of a mammal. But there is still considerable doubt whether these *in vitro* results can be directly related to conditions *in vivo*, and I⁴ have noted that "if there is indeed a limit to the mitotic potentiality of an adult tissue it is probable that this far exceeds the normal life span of the animal".

Although Hayflick's theory needs further consideration, and although there may be other important features of the mitotic tissues not yet recognized, at the moment it seems more profitable to search for an ageing mechanism in the non-mitotic tissues. The first problem is why the neurones and the skeletal and cardiac muscles are non-mitotic; by

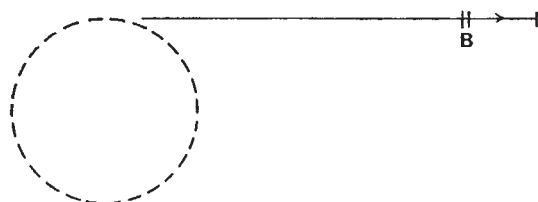


Fig. 2 Diagram of the situation in a typical non-mitotic tissue. With mitosis permanently blocked all the cells pass very slowly along the ageing pathway to their death. It is suggested that point B of the chalone mechanism (see Fig. 1) remains operative.

contrast, the smooth muscles, for example of the uterus, remain mitotic. The organization of the non-mitotic tissues is so obviously similar to that of the typical mitotic tissue that it can readily be believed that this condition is secondary. It may also readily be believed that their mitotic potential has been lost because of some advantage that this change confers, and the most obvious possible advantage is, through their decreasing efficiency, to set a limit to the life span of their owners.

On this theory it could be the rate at which the non-mitotic cells pass through the point of inhibition (Fig. 2, point B) on the ageing pathway that determines whether life is short as in a mouse or long as in a man. It is not known whether a chalone mechanism exists, in whole or in part, in any non-mitotic tissue. If such mechanisms do exist, however, one test of this theory of ageing would be to discover whether by weakening or strengthening the chalone action it is possible to shorten or lengthen the life span. From what is now known, the easiest way to strengthen the chalone action is to ensure a continuing high level of stress hormone secretion.

The first experiments showing that strengthened chalone action prolongs the life span of the post-mitotic cells were those on epidermis and sebaceous glands²⁵. Mice were subjected for many weeks to the stress of a restricted diet, which, however, was adequate to maintain full health. The result was a great enlargement of the adrenal glands and a strong inhibition of epidermal and sebaceous gland mitosis, but since neither the thickness of the epidermis nor the size of the sebaceous glands underwent any significant change it was clear that in both tissues the reduction in cell gain had been matched by a reduction in cell loss.

On the assumption that the inhibition of post-mitotic cell loss is similarly controlled in a non-mitotic tissue, it may be predicted that the rate of loss of the neurones and of the muscle cells should be reduced by any similar form of continued stress. The nervous and muscular systems should then function better for a longer period of time, the life span of the animals should be prolonged, and in particular the condition of the animals should remain relatively youthful. Experiments of this type have been performed repeatedly, though usually for other reasons, and the effects have been dramatic.

The most extensive of these experiments, using several strains of mice, were begun in 1940 by Tannenbaum and Silverstone²⁶ to test the effects of caloric restriction on tumour incidence. With a carefully restricted diet, tumour incidence fell to a low level even in high cancer strains, but more important it was also found that the dieting mice enjoyed an average life span which was 50–100% longer than that of the normal, fully fed, non-cancer-bearing controls²⁵. It was also clear that in their non-mitotic tissues there was a reduction in the rate of metabolic deterioration. This was indicated by the fact that the dieting mice remained sleek and in excellent health with active nervous and muscular systems, while the fully fed controls became senile with weak and shrunken bodies.

In this and many similar experiments subsequently carried out it was assumed that these effects were the outcome of the caloric restriction *per se*. Tannenbaum and Silverstone noted, however, that the adrenals of the dieting mice were greatly enlarged²⁷ and it has come to seem increasingly probable that both the inhibition of cancer⁴ and the promotion of longevity were the outcome of increased adrenal activity. The hungry mice lost sleep because of their continuing and stressful search for food, and in their mitotic tissues there was a reduction of both cell gain and cell loss²⁰.

If this interpretation is correct then clearly it should be possible to obtain the same effects by prolonged treatment with the stress hormones. Experiments involving adrenaline have yet to be devised (one obvious difficulty is the short life of this molecule in the circulation), but experiments with

glucocorticoid hormones have been carried out, for example by Friedman *et al.*²⁶ and Bellamy²⁷.

Friedman *et al.* began with the theory that a disturbance of the salt and water balance is an important aspect of old age, and they tested the effects of the continued treatment of 24-27 month old rats with mineralocorticoid and with glucocorticoid hormones. They found that aldosterone, the mineralocorticoid used, was badly tolerated, but that cortisol, the glucocorticoid used, prolonged the life span. They also noted that the glucocorticoid-treated rats maintained better muscle tone and better condition than did the controls.

The results obtained by Bellamy²⁷ were even more striking, since he began the treatment of his mice immediately after weaning at 3 weeks of age. The mice used were an inbred strain with an average life expectancy of only about 1 year, and they were given a corticosteroid hormone, prednisolone phosphate, in their drinking water. The result was to increase the life expectancy to an average of about 2 years, a response similar in magnitude to that obtained by Tannenbaum and Silverstone. Again the treated mice remained in excellent condition due to the reduced "rate of appearance of age-dependent characters".

All these observations support my theory but none of them is sufficiently conclusive; they could, for example, also be used to support Walford's theory²⁸ that ageing is basically an autoimmune phenomenon. But they do indicate an invaluable experimental approach to the problem of ageing in mammals. They should now be repeated and elaborated, and particular attention should be paid to the rate of neurone loss from the ganglia (the brain may be too large for accurate measurement) and to the state of the skeletal and cardiac muscles.

Role of Tissues

In mammals, it is well known that whenever the activities of a number of diverse tissues need to be accurately co-ordinated (as during an annual breeding season), it is usual for only one tissue to act as the initiator and pacemaker. In the case of ageing this would seem to be especially necessary, and if ageing is dictated by the steadily deteriorating efficiency of the non-mitotic tissues then it seems probable that one of these tissues plays the leading role. On present evidence, which is admittedly inadequate, this might be the nervous tissue, and in this connexion it is interesting how Sacher⁹ has stressed that in mammals the mass of the brain and the length of life are directly related. Certainly it is known that nervous deterioration leads to muscular deterioration and that this in turn leads to a deterioration of the circulation with repercussions so widespread as to involve all the tissues and processes of the body.

In considering senescence it is necessary to distinguish between "natural" and "unnatural" forms of death. If an animal is enabled artificially to survive into middle and old age, the natural process of ageing is seen in an increasingly exaggerated form, but simultaneously there is an increasing liability to death from a variety of pathological conditions which are unnatural in the sense that they are rarely seen in the wild. These conditions commonly arise from cell damage which can lead to tissue malfunction, to autoimmune reactions²⁹ or to local unrestrained and lethal tissue growth⁴.

At first sight the accumulation of such damage in middle age may seem to be randomly due to extrinsic influences such as chemicals, radiation and viruses, or to intrinsic faults, for example, in gene replication. But this idea of the accumulation of random damage requires some qualification. A house mouse in the second part of a life span of only 2 years is as liable to die from such pathological changes as is a man in the second part of a life span of more than 70 years, although both inhabit roughly the same environment. The fact that cell damage has remarkably little effect during the first part of life, however short or long this may be, may

indicate that at this time the damage is efficiently eliminated, for example, by the mending of broken DNA templates, the shedding of cells from epithelia and the destruction of abnormal cells by the immune response they evoke. The pathological changes of middle and old age may then represent more a deterioration in the efficiency of the repair mechanisms than a time-dependent accumulation of cell damage.

In other words these abnormal changes are more likely to be the result of senescence than its cause, and in support of this it has been repeatedly shown that the prevention of senescence by stress is accompanied by the inhibition of carcinogenesis.

My theory can be summarized as follows. In the mammals there is a mechanism which determines the time of onset of ageing and the rate at which it proceeds; this mechanism is probably based in the cells of a single tissue which acts as a pacemaker; this pacemaker is most likely to be a non-mitotic tissue and there is reason to believe that a progressive loss of neurones could of itself lead to the progressive deterioration of the whole body; cell loss is seen in all tissues and in a typical mitotic tissue it is controlled, as also is mitosis, by the homeostatic chalone mechanism; the stronger the chalone action the lower the rate of cell loss and in most tissues so far studied the chalone mechanism is strengthened whenever the concentration of the stress hormones is increased; such an increase in stress increases the life expectancy of laboratory rodents, preserves their nervous and muscular efficiency, and prevents the onset of pathological changes.

One final point may be made. If it is felt that, in order to prolong life, the imposition of stress is unacceptable, the reply may be left to Levi²⁹ who has shown that "pleasant stimuli evoking amusement are nearly as potent as unpleasant ones" in activating the human adrenals.

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Search for a Human Breast Cancer Virus

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Some human milk contains particles physically identical to the mouse mammary tumour virus. Tumorigenesis in the mouse could serve as a model in the study of human breast cancer.

CARCINOMA of the mammary gland in mouse and man was considered at one time to be primarily a hereditary disease, especially in man, because of its higher incidence in particular family groups. Bittner's discovery¹ of an extra-chromosomal factor in the milk of mice indicated that murine mammary cancer was not controlled by genes alone. Mammary tumorigenesis in the mouse was also shown to be affected by hormonal stimulation and to be modified by immune response, and the viral aetiology of this disease in mice is now firmly established. But little is known about the factors involved in the development of carcinoma of the human breast; some widely held ideas, such as the protection conferred on the mother by nursing, have recently been shattered²⁻⁴. It seems that, as in the mouse, a viral factor is involved in the aetiology of human breast cancer. Results of recent studies on human milk, some of which have been published⁵, strongly support this idea.

Human Milk

We fractionated and examined by electron microscopy milk from 212 women. The specimens can be divided into three distinct classes: 156 were from women in the Philadelphia area with no history of breast cancer in their families; ten were from women with a history of breast cancer in their immediate families; forty-six were from the Parsi community of Bombay, included because these women are three times more likely to have mammary tumour than the rest of the population of Bombay⁶⁻⁸—it accounts for 49% of all cancer⁸ although the overall incidence seems to be no greater than that in other communities⁹. Their ancestors (Zoroastrians) came to India from Persia in the seventh

century AD, and because of their strict religious rules they have married exclusively within their own small community.

By a purification procedure already described⁵ particles with the same morphological characteristics (Fig. 1) as those that cause breast cancer in mice (B particles) were found in the milk of all three groups, but the incidences in the groups were vastly different. B particles were found in the milk of seven (5%) of the American women with no history of the disease in their families; they were found in the milk of six (60%) of the Americans with a history of the disease in their families; eighteen (39%) of the Parsi women were found to contain the particles in their milk. Some details of the second group are given in Table 1. Two donors of the first group (with no family history of breast cancer) have recently provided second samples of milk after the birth of another child and B particles were again found in both. Structures different from the B particles, possibly representing various types of mycoplasma and other virions¹⁰⁻¹², were also seen in many of the isolates.

Table 1 Donors from Families with Breast Cancer History

Donor No.	Age of donor	Member of family who has had breast cancer	B particles found
1	19	Mother	—
2	24	Mother and grandmother	+
3	18	Mother	+
4	21	Mother and grandmother	—
5	26	Grandmother	+
6	30	Mother and sister	+
7	39	2 maternal aunts	—
8	27	1 maternal aunt	—
9	27	Mother	+
10	26	Mother	+

Failure to find B particles is not conclusive because of the poor sampling provided by electron microscopy.

When this investigation was started, some of the samples of human milk were frozen, but it was found that freezing greatly reduced the bioactivity of mouse milk and damaged the structure of the particles¹³. A procedure was therefore developed whereby human milk could be stored and transported at room temperature. The procedure consisted of

adding to the fresh milk an equal volume of a solution containing 400 U of penicillin G, 2,000 μ g of neomycin, 100 μ g of acromycin, and 200 U/ml. of polymyxin B. Mouse milk prepared in this way could be kept for 5 days at 37° C and for months in the refrigerator without noticeable change in the virions. There was also little change in bioactivity in mouse milk after storage at 37° C for 8 days (Table 2). Bentamycin (Schering, 0.01 ml./ml. of milk) is also a satisfactory preservative.

many tumour virus (MTV) antigens, but not whole virions, have been reported in spleen cells²³ and Leydig-cell tumours (unpublished results of R. C. Nowinski, N. H. S., L. J. Old, D. H. M. and J. Hilgers), but there is no evidence for a causal relationship between MTV and any neoplasm except that of the mammary gland.

Explants of mouse mammary tumours have been grown in culture for many years^{24,25} and a few cell lines have been established²⁶. The cells proliferate virus to varying degrees²⁷.

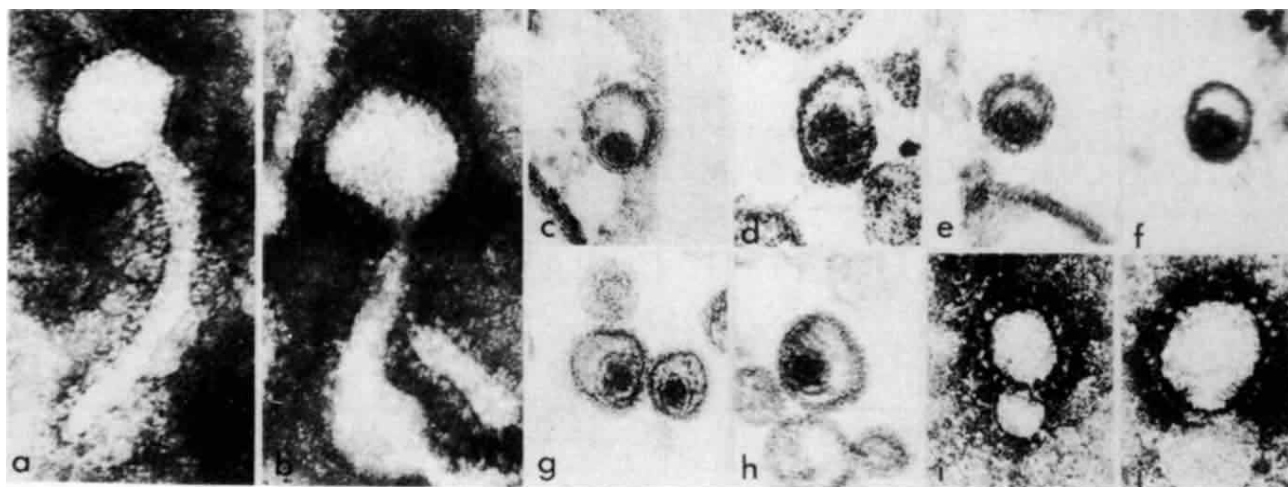


Fig. 1 Particles found in human and mouse milk and in culture fluid. *a*, Negatively stained particle from American human milk; note the long curved tail and knobbed surface protrusions. *b*, Negatively stained particle from RIII mouse milk ($\times 180,000$). *c*, *d*, *e* and *f*, Thin sections of particles from Parsi milks ($\times 90,000$). *g* and *h*, Thin sections of particles from RIII mouse milks ($\times 90,000$). *i* and *j*, Negatively stained particles from fluid of human breast cancer cell culture, but found also in foetal calf serum ($\times 200,000$).

The structure of the intact MTV virion is distinct from all other known structures^{5,14}. In negative contrast, the well preserved virion forms a head about 100 m μ in diameter and a tail of variable length. The surface projections on the membrane are different to those of myxo- and paramyxoviruses. They are also different from the projections on mitochondrial membranes and from those of any other cellular membrane¹⁴. They are a little less than 100 Å long and they consist of a stalk 10 to 20 Å in diameter with a 50 Å knob at the distal end. These projections are spaced over the surface of the particle at a centre to centre distance of 70–75 Å.

B Particle and Tissue Culture

Usually virions replicate in the mammary gland¹⁵ or mammary tumours, but proliferation has also been seen in male genitalia¹⁶, thymus¹⁷, thymic¹⁸ and lung¹⁹ tumours and in transplanted mouse ependymoblastoma²⁰. Virions and bioactivity can be detected in blood^{21,22} and bioactivity can be detected in all tissues of high-tumour-strain mice. Mam-

It has not yet been possible, however, to infect any virus-free cultures with the mouse virus and obtain virion proliferation²⁸. Until recently most specimens of human breast cancer obtained from surgery have not survived explantation and few cell lines have been established²⁹. The availability of collagenase and new standardized culture media have eliminated most culture problems and permit routine explantation of human breast tumours. Collagenase treatment liberates cancer cells from collagen fibres and prevents overgrowth by connective tissue cells³⁰.

Particles covered with knobbed protrusions have been found in culture fluids of primary breast carcinomas¹. Although these structures have envelopes somewhat similar to those only associated with mouse B particles, they have neither the characteristic size nor shape (Fig. 1, *i* and *j*) and are therefore not considered to be B particles. Identical structures have been observed consistently in concentrates of pooled commercial bovine sera used in the cultures.

Complexity of the Mouse Model

From the beginning of the twentieth century until the early 1930s, while isogenic strains of mice were being developed, it was generally concluded that the occurrence of mammary carcinoma was determined principally by genetic constitution, but in 1933, that reciprocally cross-bred mice of high and low strains were observed to have a cancer incidence that did not follow the laws of Mendelian genetics, but depended primarily on the mother^{32,33}. Thirty-five years have passed since Bittner's discovery of the milk factor and, in spite of hundreds of attempts to identify and isolate this factor^{34–37}, general agreement has been reached on its identification^{38–45} only recently. The reasons for the long period of frustration are varied, but the difficulties were finally overcome by recognizing that low-tumour-incidence mice

Table 2 Assays of Incubated Mouse Milk

Treatment	No. positive/No. at risk (%)	
	Dilution 10 ⁻³	Dilution 10 ⁻⁴
Fresh	2/8 (25)	4/6 (75)
24 h at 37° C	10/10 (100)	10/12 (83)
48 h at 37° C	6/7 (86)	5/10 (50)
96 h at 37° C	8/8 (100)	3/9 (33)
192 h at 37° C	4/12 (25)	6/11 (55)

Skim milk from strain RIII mice was assayed for infectivity in C57CL/Haag mice by the detection of viral antigen in their milk at the third lactation⁴⁸. Before incubation, antibiotics were added to the RIII milk (see text).

were carriers of MTV which could be potentiated by hormones or other means and that the male sometimes transmitted the virus. More rapid assay procedures⁴⁶⁻⁴⁹ and improved methods of isolation were developed, and finally, by titrations of isolates, a correlation was found between infectivity and a specific particle¹³ (Table 3).

Table 3 Correlations of B Particle Count with Infectivity

Gradient band	ID ₅₀ /0.1 ml.	Antilog ID ₅₀ /0.1 ml.	B particles/100 EM quadrants	B particles/antilog ID ₅₀
(1)	10 ^{-0.57}	7.6	50	6.6
(2)	10 ^{-1.35}	54	2,800	51
(3)	10 ^{-2.25}	400	10,000	25
(4)	10 ^{-0.75}	8.8	620	70
(5)	10 ^{-0.56}	7.5	450	60

Resuspended ultracentrifuged pellet from RIII milk was centrifuged on a preformed linear Ficoll density gradient. The contents of the tube were divided into five fractions or bands from top to bottom (column 1). The infectivity of each fraction (column 2) was correlated with B particle counts (column 4) and in the last column the ratio of particles to infectivity was shown to be constant within the errors of the procedure. In band 1, the B particles were difficult to count because of fat globules.

Knowledge of the mouse mammary tumour virus and its role in tumorigenesis can be summarized as follows. (1) Mammary adenocarcinoma has been extensively studied in about a dozen inbred mouse strains. Low tumour strains with a tumour incidence of 0-5% in females and high tumour strains with an incidence of 95-100% as well as strains with intermediate incidences have been developed. (2) Reciprocal crosses between low and high tumour strains produce offspring with an incidence similar to that of the mother^{32,33}. There are exceptions, however, and it is concluded that some fathers can transmit the virus and indeed virus particles can be found in male genitalia¹⁶. (3) Usually the tumour incidence and tumour characteristics can be greatly influenced by foster-nursing newborn litters; that is, the fostered litters tend to have the tumour incidence and tumour characteristics of their foster mothers^{1,50}. Again there are exceptions: the litters of two strains GR and C3H-A^{vy}fB retain the high incidence (95-100%) in spite of being fostered on tumour-free strains^{51,52}. This has been attributed, with good evidence, to the integration of the viral genome into the sex cells of the parents⁵³. (4) Mouse mammary carcinoma is usually transmitted from mother to daughter in the mother's milk. Milk of high cancer strains contains from 10⁹ to 10¹² virus particles per ml. and infectivity remains at 10⁻⁵ to 10⁻⁸ dilution. Evidence for natural horizontal transmission is lacking; it is not a contagious disease. (5) Tumorigenic activity may be related to a particular virus particle readily recognizable under the electron microscope. The existence of a sub-viral active entity or a provirus is not yet fully established, and the question of an inhibitor is not settled³⁷. (6) The virus seems to be an essential factor in tumour development, but not all mice carrying the virus develop tumours; other factors⁵⁴ greatly influence tumour development. Mice carry the virus from infancy when they obtain it in their mother's milk, but they do not usually develop the disease until middle age or later and in some virus-infected strains many never do⁵⁵. (7) It has been possible neither to transfer the virus to any other species nor to infect any normal cells in culture.

Mouse Model applied to Humans

The extensive mouse studies have been made, of course, for the purpose of gaining knowledge of the human disease. There are striking similarities between the disease in the two species. In both there are family groups: in the case of

mice this was first recorded by Murray⁵⁶ at the beginning of this century. At that time there were no inbred mouse strains, but by selective breeding experiments begun in 1906, Murray obtained an incidence of 18.1% among progeny of cancerous ancestry compared with 8.3% among offspring of non-cancerous ancestry. Ninety-nine female wild house mice bred in the laboratory by Andervont⁵⁷ for 10 yr had a mammary tumour incidence of about 6%, little different from that in American women. Although insufficient milk from wild mice has been obtained to confirm the presence of virus particles, it has been shown to contain a milk factor: when a low tumour strain of laboratory mice (BALB/c) was fostered by them, the BALB/c mice became infected and took on the characteristics of a high tumour strain; these fostered mice remain one of the best producers of MTV⁵⁸.

Penrose *et al.*⁵⁹ studied the incidence of breast cancer in human families and found that there was a significantly greater incidence among mothers and sisters of 510 breast cancer probands but no increased frequency in either sex from other types of malignancy. Similar results were obtained by Smithers *et al.*⁶⁰. In an investigation of 544 women suffering from breast cancer, Anderson *et al.*⁶¹ concluded that sisters of breast cancer patients develop the disease at a rate 1.8 times higher than the controls. Of 1,802 patients of Haagensen⁶², 25.8% had female relatives with a history of breast cancer; 9% of the patients' mothers had the disease.

Serious cases of cancer families have been reported for more than 100 y. In 1866 Paul Broca, a French surgeon, reported that ten of the twenty-four women of his immediate ancestors died of breast cancer. Families in which carcinoma of the breast has occurred in three successive generations have frequently been reported. Papadrianos *et al.*⁶³ state: "The simplest of the many different aspects of familial inheritance is the frequency of the disease in mothers, daughters and sisters of women who develop it". Although some data do not confirm the familial nature of human breast cancer, Clemmesen⁶³, the leading authority on the statistics of cancer, concludes: "It is difficult to avoid the impression that the scale of such studies . . . has not reached a size matching their task. . . . Nevertheless, as a general conclusion it would seem that heredity of breast cancer has in man been found too often to be explained as due to co-incidental occurrence, and is probably as real as in the mouse".

Table 4 Breast Cancer Incidence Rates

Location	Incidence rate
Bombay (Parsi)	51.5
Boston, US	55.0
Glamorgan County, Wales	38.8
Athens, Greece	28.9
Slovenia, Yugoslavia	24.4
Taipei, Taiwan	9.1

Cases per year per 100,000 female population³. Japan has approximately the same incidence rate as Taiwan.

It must be pointed out that hereditary and viral transmission is not distinct even in the mouse and much less so in humans; however, most cases of mammary tumour inheritance in mice have been traced to the virus or viral genome.

Mice develop multiple primary tumours, a characteristic which is not thought to be shared by humans, but Haagensen states (personal communication) that of 626 of his patients, studied for a minimum of 10 yr, thirty-six developed a new primary carcinoma of the other breast. The number of cancers of the other breast that would have been expected

on the basis of age specific rates for cancer of one breast is 4.9.

The development of mammary carcinoma in both mice and women is influenced by hormones but the influence is complicated. When Lacassagne⁶⁴ induced mammary tumours in male mice by the administration of oestrogen in 1932, it was thought that oestrogen might be carcinogenic, but experimentation of the intervening years has led to the conclusion that hormones are only promoting factors and that an initiating agent such as the mammary tumour virus is always necessary⁶⁵. Specialists in cancer of the human breast have come to the same conclusion; hormones alone cannot initiate cancer.

Effect of Nursing

It has long been held that lactation had a significant prophylactic effect on breast cancer, because in countries in which it is rare, nursing is customary and frequently prolonged. Furthermore, there has been an increase in breast cancer in recent years associated with a decrease in breast feeding. A number of studies²⁻⁴ indicate that there is no relationship between the incidence of breast cancer and lactation. The great variation in breast cancer incidence in the different areas of the world, shown in Table 4, is still unexplained. It is possible that, as in the mouse, a mammary tumour virus has something to do with it, and that low, intermediate and high cancer populations have developed naturally.

Implications of Mouse Model

We conclude that the similarities between adenocarcinoma of the breast in mice and women are too extensive to be coincidental and that human breast cancer may also be a viral disease. Moreover, recent studies suggest that human virus may be similar to if not morphologically identical with the mouse virus; sera from breast cancer patients have a neutralizing effect on the mouse virus whereas control sera do not⁶⁶. The mouse model suggests several modes of attack on human breast cancer, although controlled infection studies in which animals are inoculated with infective material, the most productive approach in the mouse, are of course impossible to pursue in man. Retrospective and prospective statistical studies of breast cancer incidence in women, lengthy and unsatisfactory as they may be, can provide data consistent with the notion of vertical transmission of a tumour virus. Other approaches found useful with mice are more promising. Examination of particles similar to or structurally identical with mouse virus by electron microscopy and immunological studies are providing evidence of the existence of such entities in human material. The existence in milk and tumour extracts of antigens related to mammary tumour virus has been demonstrated by means of gel immunodiffusion⁶⁷ and by agglutination inhibition of tanned red cells coated with purified virus antigen⁶⁸. Polymerases peculiar to the tumour viruses⁶⁹⁻⁷¹ have been found by Spiegelman and Schlom in the mouse virus. Similar demonstrations may be possible with the human virus. Apart from these efforts to demonstrate a virus as the aetiological agent in the human disease, an attack on the tumorigenic process in mice by immune therapy prophylaxis or chemotherapy (including the use of interferon⁷² or interferon inducers) seems important since a successful method might be developed for the mouse that could be tested, with minimal risk, in women.

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Colour and Brightness Preferences in Monkeys

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A method has been developed for testing the preferences of monkeys for simple visual stimuli. Preliminary results for colour and brightness have already been obtained.

THE basis of people's everyday decisions is usually "aesthetic" preference. Clothes are chosen for their colour; a bar of soap is chosen for its smell; the route of a journey is chosen for the scenery along the road. Very little is known, however, about these preferences—the stimuli that are preferred cannot be specified in any detail; it is not known how far they depend on genetic, developmental and cultural factors; almost nothing is known about their evolutionary history and little about what biological advantage they bring.

With these general questions in mind, I have investigated the preferences of male rhesus monkeys (*Macaca mulatta*). It is of theoretical importance to know whether any comparable phenomena occur with lower primates. If they do, there will be the practical advantage of being able to study some of the central questions I have listed in an experimental animal, which can be subjected to environmental and physiological control. I have begun by looking at preferences for simple visual stimuli, and wish to describe a method and some preliminary findings.

In studies of "sensory reinforcement" such as those of Butler¹, sensory stimuli have been made the primary goal of the animal's behaviour. I have chosen, instead, to study what happens when the stimuli are made incidental to behaviour which already has an independent goal. I have given a monkey a free choice of alternative behavioural routes to obtain food, each of which is equally efficient but involves exposure to different visual stimuli: to the extent that the monkey chooses one route rather than another, he shows a preference for the associated stimuli.

A monkey was put in a testing chamber where visual stimuli could be back-projected on one of the walls. The chamber contained a single response key and the monkey was rewarded with food for holding down this key for a cumulative period of 100 s, independently of his detailed pattern. The key controlled the presentation of the visual stimuli and the programme ran as follows. In any particular session there would be two alternative stimuli, say *X* and *Y*, which would be produced alternately by successive holds on the key. When the monkey pressed the key first he might get *X*, which would stay on as long as the hold was maintained; when he released the key and pressed again he would then get *Y*, which, likewise, would stay on as long as the hold was maintained; the next press would produce *X*, the next *Y*, and so on. To exercise a preference the monkey had simply to hold the key down when he preferred the current stimulus and release and press again when he did not.

The testing chamber (Fig. 1) was a small rectangular box, 80×65×45 cm, painted black inside. At one end of the chamber, covering the wall, was a ground glass screen, 45×45 cm, on which the alternative stimuli were projected from either of two projectors. The stimuli could be varied by changing the slides in the projectors. Bars across the chamber confined the monkey to a relatively small compartment at the opposite end to the screen so that he sat facing the screen at a convenient visual distance from it, about 40 cm. In front of him was a sloping dashboard bearing the response key and

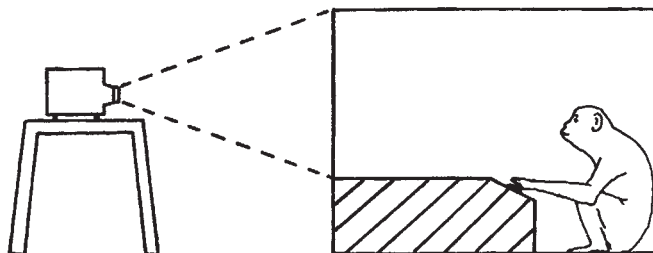


Fig. 1 Testing chamber.

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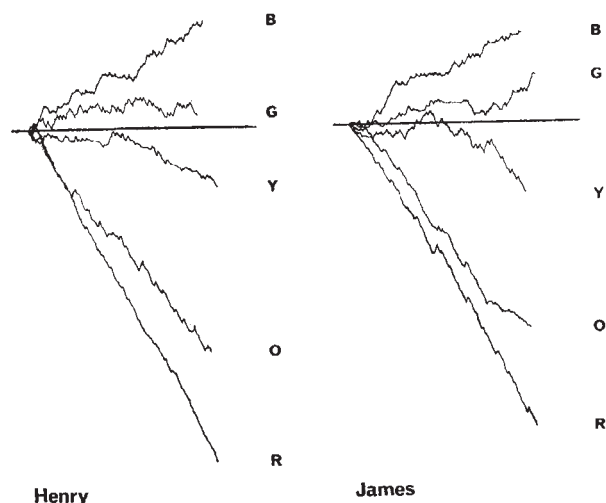


Fig. 2 Sample records from tests for colour preference. The test stimuli were homogeneous coloured fields of equal subjective brightness, paired in each case with a standard white field of the same subjective brightness. The lines show how the monkey divided his time between the test and the standard stimuli: the recording pen moved upwards at 75° when the test stimulus was on and downwards at 75° when the standard comparison stimulus was on, so that upward slopes represent positive preference and downward slopes negative preference relative to the standard. B, blue; G, green; Y, yellow; O, orange; R, red.

below that was a pellet tray. In the roof was a small pea-bulb which served as a dim houselight during time-out periods. When the monkey first entered the chamber the houselight was on and the response key was inoperative. After a short while the houselight went out and the response key became effective. The monkey was then free to press the key as he chose, alternating between the two stimuli and holding either as long as he wished, although with the constraint that neither was to stay on longer than 10 s or else it was automatically terminated and he had to release and press again (in practice this limit was very rarely reached). When he had clocked up 100 s of total response, the houselight came on again and the key was inoperative for the next 50 s during which time five banana pellets were delivered to the tray. The houselight then went out, the key became effective and the programme was recycled. At the end of ten such cycles (1,000 s of total response), the houselight came on finally and the sequence was terminated. In the course of the experiment measurements were made of the total number of alternations between the two stimuli and the total time spent in the presence of each. The monkey's performance was also displayed on a pen recorder which showed from moment to moment how he divided his time between the two stimuli: the recording pen moved upwards at an angle of 75° degrees when one stimulus was on and downwards at an angle of 75° degrees when the other was on, so that the overall slope indicated the preference.

The principal results obtained so far concern colour and brightness preferences. The stimuli here were homogeneous fields of light filling the whole screen, with brightness and colour determined by filters in the projectors. For the brightness study the fields were white and ranged in brightness in eleven steps from 0.1 to 1.7 log foot-lamberts. For the colour study the fields were coloured red, orange, yellow, green and blue (Kodak Wratten filter numbers 25, 22, 12, 58 and 38A, respectively) and were adjusted in subjective brightness with an SEI photometer to 0.9 log foot-lamberts for the human eye, which has a sensitivity curve almost identical to that of the rhesus monkey². So that all measurements of preference should be directly comparable, a white field of 0.9 log foot-lamberts was used as a standard stimulus with which to pair each other stimulus to measure the relative preference.

Four monkeys, all adolescent males imported from India about one year previously, took part in this experiment. Outside the testing sessions they were housed in pairs in cages in the home colony and were fed on a diet of chow which was freely available. One pair, Henry and James, had more extensive testing than the others, and the results for these two will be given in detail. They were tested 6 days a week, twice a day, for colour preference in the morning and for brightness preference in the afternoon. The different levels of brightness and the different colours were tested in a random order which was the same for both monkeys. The set of brightness stimuli was run through twice consecutively and the set of colour stimuli three times, that is, for each level of brightness two measurements were made separated by about 2 weeks, and for each colour three measurements separated by about 1 week.

About 15 days' training with irrelevant stimuli was given to familiarize the monkeys with the contingencies of the testing situation. With this preliminary experience the pattern of performance settled down and became very constant. The monkeys responded usually without interruption and completed the 1,000 s of stimulus presentation in about 1,300 s (not counting time-out periods). During this time they alternated rapidly between the two stimuli, on average about 400 times. The number of alternations was higher overall for the brightness tests than for the colour tests (means of 439 and 354, respectively: $P < 0.01$ on a t test), but otherwise it had little relationship either to the nature of the stimuli or, surprisingly, to the degree of preference shown: an increase in preference could mean either an increase in the time for which the preferred stimulus was held on or a decrease in the time for which the non-preferred stimulus was held on, and the sum of these periods—the time for two alternations—need not, and did not, vary systematically. The preferences tended to be quite stable from the beginning to the end of a session; there were no marked swings, and the monkeys showed little sign of losing interest in the stimuli even when the sessions were extended to twice their usual length. Rapid alternation in combination with a basically stable preference led to almost linear performance records.

Figs. 2 and 3 show for Henry and James some sample records from individual sessions, and Fig. 4 shows the mean

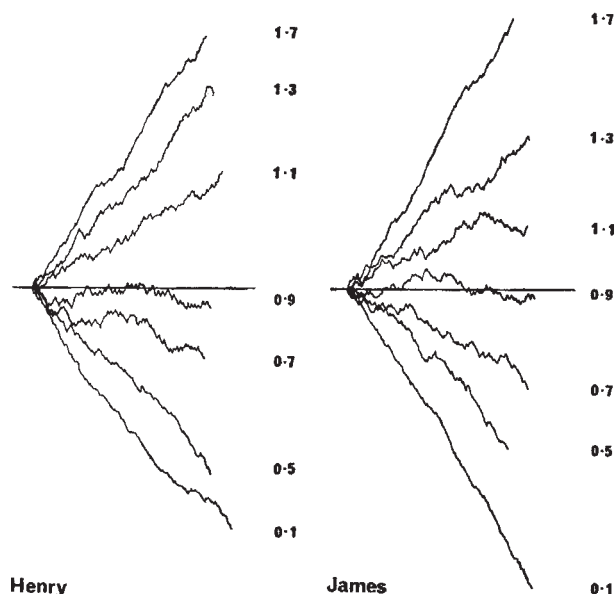


Fig. 3 Sample records from tests for brightness preference. The test stimuli were homogeneous white fields of different brightness. The numbers give the brightness of the test stimuli in log foot-lamberts.

preferences for each test stimulus in terms of the amount of time per 1,000 s session spent with that stimulus as opposed to the standard stimulus. Table 1 gives the results of three-way analyses of variance on the preference and alternation scores.

Table 1 Results of Three Way Analyses of Variance

A Preference scores		
Source of variation	Degrees of freedom	Variance ratio
(i)		
Brightness levels	10, 10	509 *
Repeated measurements	1, 10	3.13
Monkeys	1, 10	0.00
(ii)		
Colours	4, 8	112 *
Repeated measurements	2, 8	0.45
Monkeys	1, 8	0.02
B Alternations		
Source of variation	Degrees of freedom	Variance ratio
(i)		
Brightness levels	10, 10	0.77
Repeated measurements	1, 10	1.05
Monkeys	1, 10	1.03
(ii)		
Colours	4, 8	0.51
Repeated measurements	2, 8	0.87
Monkeys	1, 8	2.79

* Significant at 0.1% level; no other results were significant at 5% level.

Both monkeys had strong preferences related to both brightness and colour. These preferences were not, as might have been expected in a two-choice situation, all or none, but were finely graded. The brightness preferences were monotonically related to brightness over the range used, and, more surprisingly, the colour preferences were monotonically related to wavelength. Repeated measurements were highly consistent, and there was remarkably little variation even between the two monkeys.

The other pair of monkeys, who were actually rather younger than Henry and James, showed similar strong and reliable

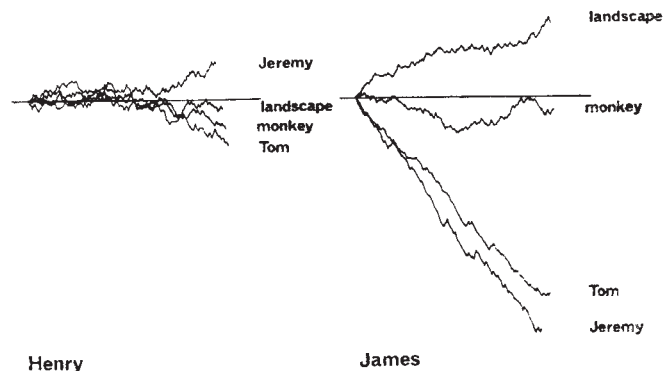


Fig. 5 Sample records from tests for picture preference. The test stimuli were coloured photographs of equal subjective brightness to the standard stimulus. Jeremy, the laboratory photographer; Tom, the animal cleaner; monkey, a frightened monkey in a cage; landscape, a mountain in Connemara.

preferences. Their preferences were quantitatively close to those of Henry and James in the case of brightness, but were smaller in the case of colour, although the same rank order of colours obtained.

To follow up the striking similarity in the behaviour of the different monkeys, I made additional tests with other kinds of stimuli. It was found, predictably, that with more complex and meaningful stimuli this similarity no longer held. Fig. 5 shows sample records from sessions where the stimuli were "pictures" instead of homogeneous fields. The pictures were coloured photographs of people, animals and outdoor scenes, adjusted in overall brightness (when defocused) to 0.9 log foot-lamberts; as before, each was compared with the standard white field. With these stimuli the preferences of individual monkeys diverged. Henry, for example, was relatively indifferent to a picture of Tom, the cleaner, whereas James apparently disliked it; of the other monkeys, one strongly liked the same picture, whereas the other disliked it as much as James.

These results as a whole show the method to be an effective way of demonstrating and measuring visual preferences. The specific findings raise many points for further exploration. (1) To what extent, if at all, are the demonstrated preferences peculiar to this testing method? In particular, what is the significance of using primary reinforcement to maintain the key pressing behaviour? Would the results have been the same had some other reward than food been used or had it been practicable to use no reward at all? (2) What are the formal characteristics of the preferences? For example, if stimulus *A* is preferred to *B*, and *B* is preferred to *C*, does it follow that *A* is preferred to *C*? Or, if stimulus *D* is strongly preferred to *E* and only weakly preferred to *F*, does it follow that *F* is preferred to *E*? (3) What is the origin of the preferences? Can the similarity in the brightness and colour preferences of different monkeys be taken to mean that these preferences are species-specific and independent of individual experience, or could it be that these monkeys happened to have had the same experience at some critical period in their early life? (4) How far are the preferences a function of a particular set of environmental and bodily conditions? How would they be affected, for example, by changes in ambient temperature, changes in time of day, or changes in motivational state? (5) What is the adaptive value of the preferences? In so far as they are innate, what significance do they have for a monkey in the wild?

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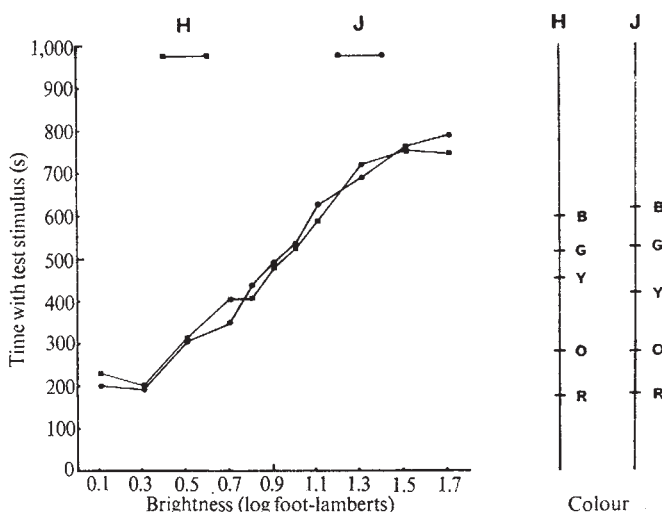


Fig. 4 Mean preferences on the brightness and colour tests, averaged over two sessions for brightness and three sessions for colour. The ordinate gives the amount of time per 1,000 s session spent with the test stimulus as opposed to the standard stimulus.

LETTERS TO NATURE

PHYSICAL SCIENCES

Terrestrial Spectroscopy by a Cryogenic Gravity Meter

LATE in the nineteenth century and early in the twentieth century, British scientists such as Lamb¹ and Love² had made theoretical predictions about the free oscillations of the Earth. The gravest mode was calculated to be about 1 h. Benioff³ in 1954 surmised that a signal with a 57 min period recorded during the Kamchatka earthquake might be the grave mode of the free oscillations of the Earth. Pekeris⁴ and his colleagues, stimulated by such predictions, were able to calculate the period of free oscillations of the Earth for a large number of modes, and these theoretical predictions were confirmed for the first time^{5,7} after the great Chilean earthquake of May 22, 1960. Easier numerical integration techniques for calculating different models of the Earth have since been introduced⁸ and other earthquakes—among them, the Kurile Islands earthquake⁹ of October 13, 1963, the great Alaskan earthquake¹⁰ of 1964 and the Rat Island (Aleutians) earthquake¹¹ of February 4, 1965—have confirmed some of the observations made during the Chilean earthquake. Recently, it has been possible¹² to record the spheroidal oscillations of the Earth from earthquakes of magnitude 6.5.

I have been developing a cryogenic gravity meter in the past 5 years¹³ with the cooperation of Professor William Fairbank of the Stanford University physics department. With this instrument, we have recorded a large number of spheroidal oscillations of the Earth over three different periods. The signal ranges from 2 dB to 9 dB above the mean of the record. Several of these peaks are over the 95% confidence limit.

The instrument has a 1 inch hollow niobium sphere suspended in a cylindrically symmetric magnetic field with a suitable magnetic gradient. The superconducting hollow sphere behaves as a diamagnetic element. The magnetic field and the field gradient are adjusted so that upward magnetic push on the ball is balanced by the pull of gravity. In

this way, the hollow sphere is freely suspended at the centre of the instrument. The initial raising of the ball is monitored by a special photosensitive device which can operate at liquid helium temperature. The magnetic field and the field gradient are produced by superconducting coils which are made persistent after adjusting the datum of the hollow sphere. A mu-metal canister and a niobium cylinder serve to shield the instrument from external magnetic perturbations.

An independent detection module, using a double Josephson's junction (also known as SQUID) (see ref. 14 and also A. Hebard, personal communication), senses the flux change produced by the motion of the hollow sphere. (The hollow sphere in this present arrangement is immersed in liquid helium.) The detection module can sense a motion of less than one Angström (0.1 nm). A feedback circuit provides a sufficient negative signal so that the Josephson's junction effectively remains in the same magnetic environment, which is accomplished with the aid of a phase-sensitive detector. The system has been calibrated and has proved to have a large linear dynamic range. A portion of the signal is fed to a chart recorder, which depicts the true motions of the suspended sphere. The system has a theoretical sensitivity of about 15×10^{-12} cm/s². No measurable drift of the detection module has been recorded over the period of 2 h when the instrument is functioning properly (my unpublished observations).

The analog records obtained from a chart recorder are digitized, after which a Fourier transform is performed on the data. A close inspection of the plot of the period and amplitude of the data reveals four independent types of evidence, indicating that the spheroidal oscillations of the Earth have been recorded continuously at Stanislaus State College. These evidences are discussed below.

(1) A large number of the strong peaks coincide with the observed periods reported by other investigators. However, this evidence can be questioned, since some unknown strong peaks also have been observed that may be overtones. As far as I know, they have not yet been reported by other investigators (Figs. 1, 2 and 3).

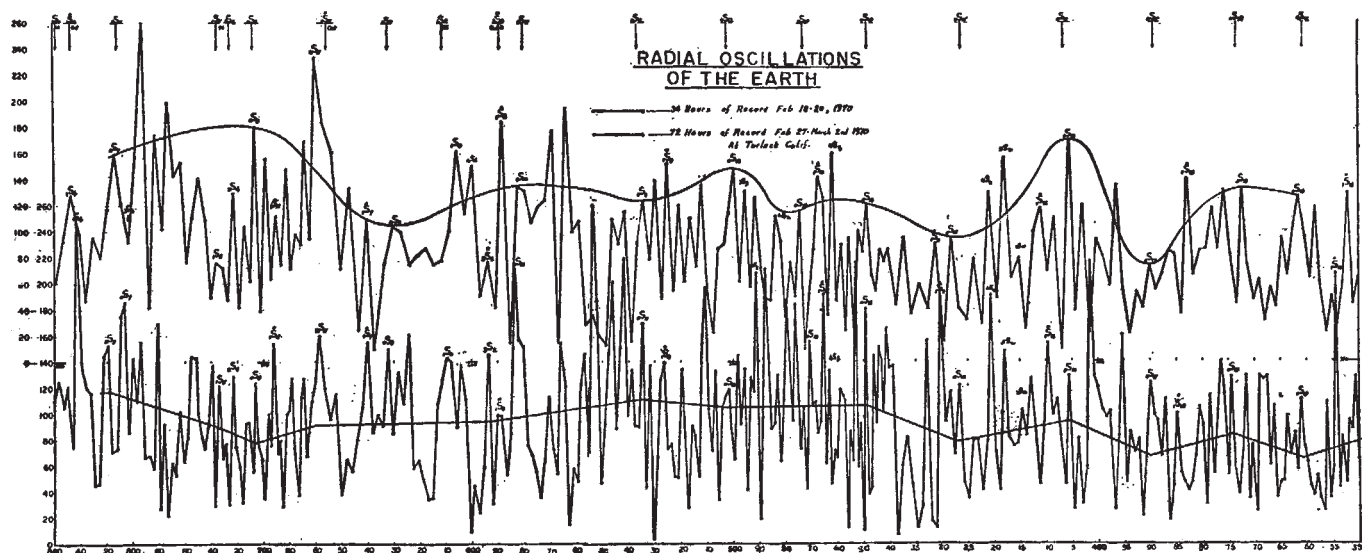


Fig. 1 Radial oscillations of the Earth. Top: 34 h of record February 18–20, 1970. Bottom: 72 h of record February 27–March 2, 1970.

(2) In all three independent records of February 18–20, February 27–March 2, and July 31, 1970, I have observed clearly the splitting of the $0S_2$ mode. (In the three experiments, continuous records were obtained for 32, 72 and 18 h respectively.) Inevitably, the main line is observed as a trough. This splitting, which is due to Earth rotation, should and did

yield a trough for the main line of 3,233 seconds because of the geographic location of Stanislaus State College. Similar splitting is observed for the $0S_3$ mode. This independent evidence cannot be taken as a chance, since it has been observed repeatedly over three independent observations (Fig. 4).

(3) A striking feature of the first two recordings which are

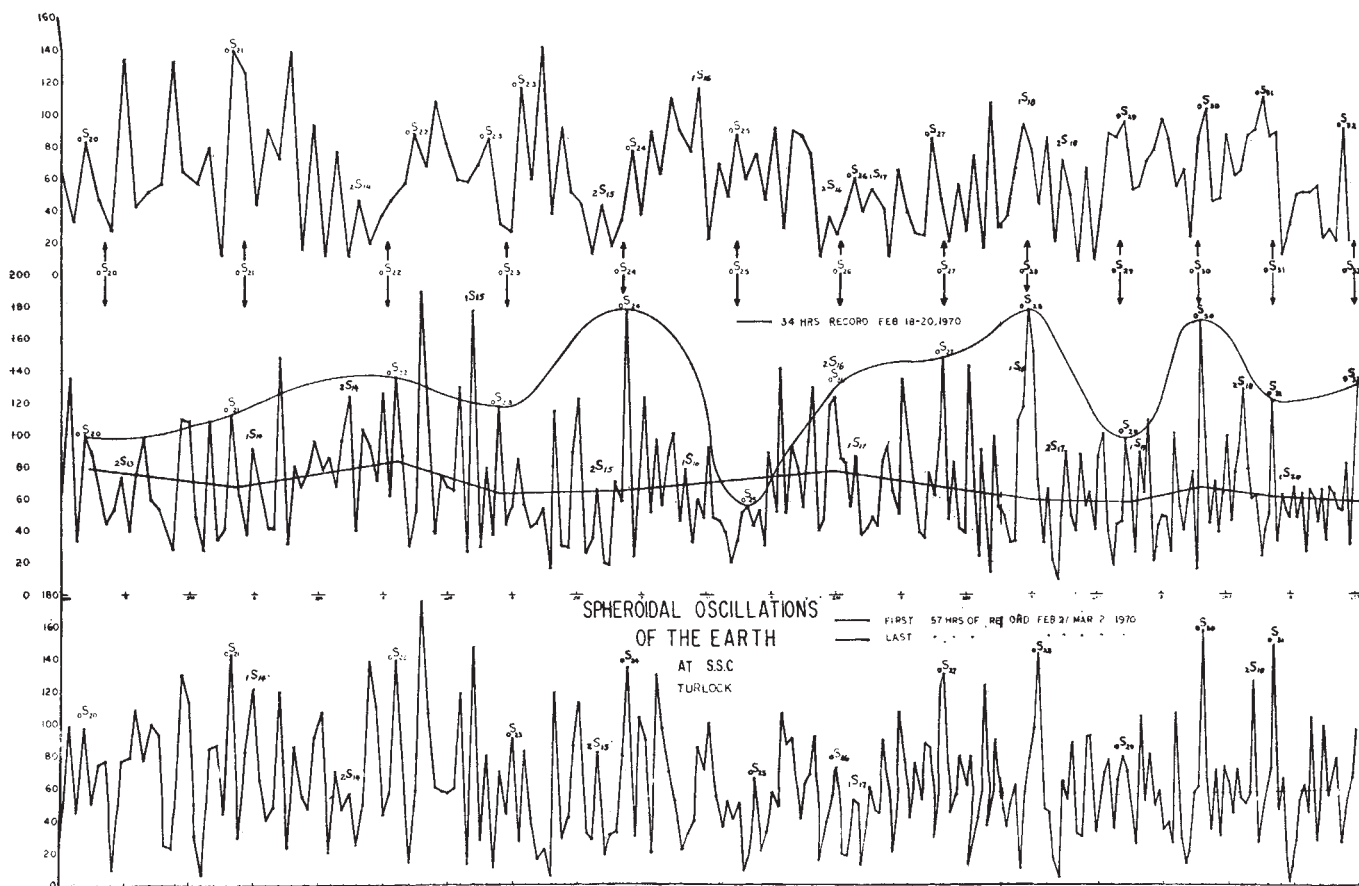


Fig. 2 Spheroidal oscillations of the Earth. Top: 34 h of record February 18–20, 1970. Centre, first 57 h and, bottom, last 57 h of record February 27–March 2, 1970.

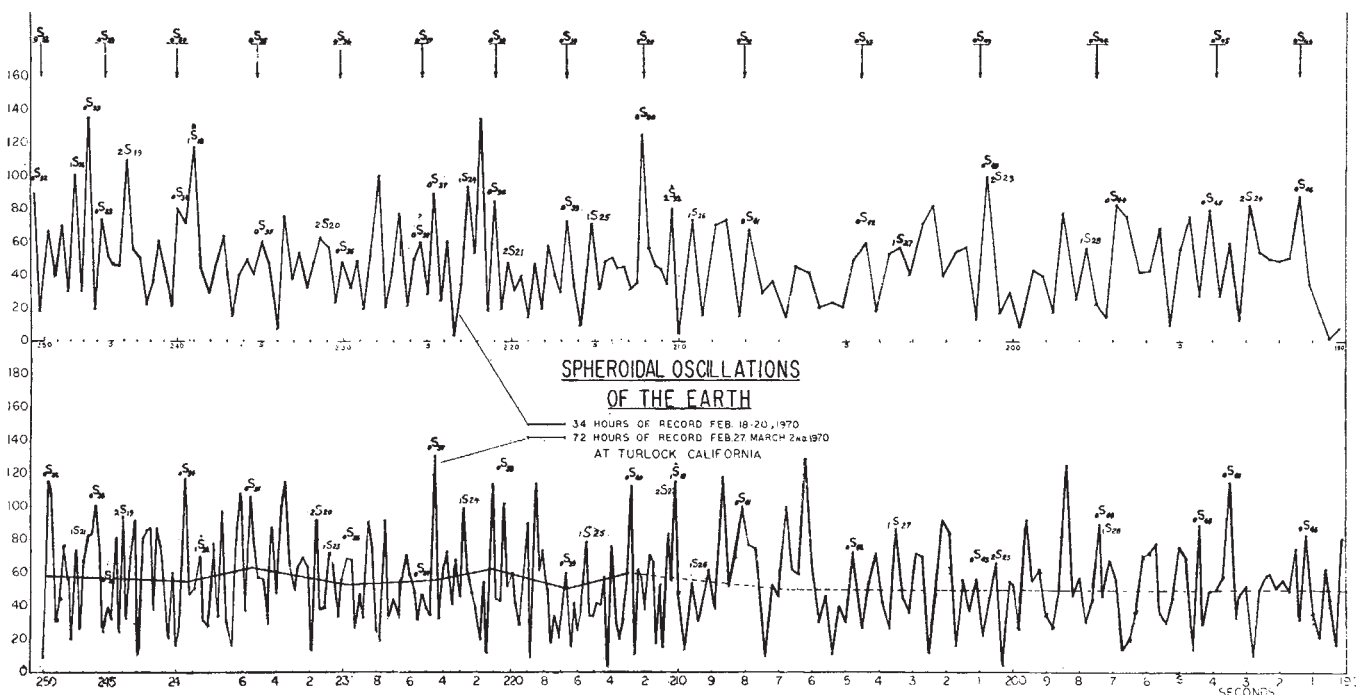


Fig. 3 Spheroidal oscillations of the Earth. Top: 34 h of record February 18–20, 1970. Bottom: 72 h of record February 27–March 2, 1970.

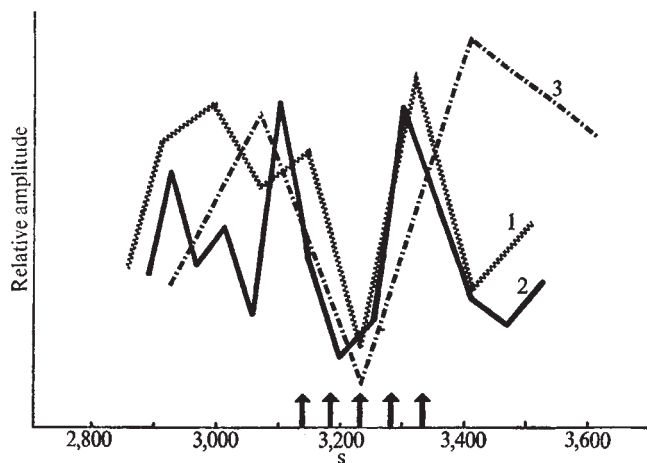


Fig. 4 Degeneration of oS_2 due to Earth rotation. Experiment 1, February 18–20, 1970. Experiment 2, February 27–March 2, 1970. Experiment 3, July 31, 1970. Degeneration $2l+1$; $l=2$; number of lines = 5.

reported here are the variations of amplitudes as we move from even harmonics to the odd harmonics. In the first experiment, during February 18–20, 1970, it was observed that the even harmonics from oS_8 , oS_{10} and all the way to oS_{18} have consistently higher amplitudes when compared with oS_9 , oS_{11} and oS_{19} . In the second experiment, the same phenomenon is observed in the region of oS_{20} to oS_{32} , where

Table 1 Measured oS_n Modes (Periods in Seconds)

n	Present observations				John Derr ¹⁵
	F. Press ¹⁵	Series 1	Series 2	Series 3	
0	1,227.64	1,228.80	1,233.70		
2	3,237.0	3,233.0	3,233.0	3,233.68	3,233.30
3	2,137.2	2,118.6	2,133.33	2,118.60	2,133.56
4	1,549.2	1,536.0	1,551.5	1,536.0	1,547.16
5	1,191.6	1,193.0	1,197.7	1,204.7	1,193.30
6	964.2	975.23	957.0	960.0	963.94
7	811.2	813.77	806.3	808.4	811.67
8	705.6	706.20	706.2	706.2	707.57
9	634.2	630.15	632.09	633.4	634.01
10	577.74	582.37	583.47	579.6	580.04
11	535.02	534.26	534.72	534.2	536.46
12	501.72	499.51	501.96	503.6	502.03
13	472.50	474.44	471.89	472.6	473.05
14	447.90	448.46	449.12	448.46	448.37
15	426.12	428.15	426.66	426.66	426.19
16	406.68	405.54	405.54	406.88	406.54
17	389.52	390.09	390.09	388.86	389.37
18	373.86	372.36	374.40	372.36	373.39
19	358.88	360.35	361.20	359.28	360.57
20	346.68	345.17	349.48	349.09	347.39
21	335.70	336.65	336.84	335.70	335.80
22	324.60	322.52	324.05	323.37	325.07
23	315.36	316.70	315.56	315.08	315.11
24	306.30	305.67	306.12	305.67	306.10
25	297.54	297.53	297.0	too low	297.54
26	289.62	288.45	290.08	289.8	289.48
27	281.64	282.46	281.71	280.5	282.38
28	275.28	275.51	274.90	273.1	274.87
29	268.14	267.71	267.71	267.13	268.27
30	262.08	261.45	261.89	261.44	261.94
31	255.96	257.07	256.32	254.94	256.02
32	250.02	250.78	249.75	249.75	250.09
33	245.10	246.74	246.15	244.78	245.30
34	239.52	240.00	239.53	239.06	239.87
35	235.20	234.95	235.67	234.50	234.51
36	229.74	230.11	229.85	229.2	229.66
37	224.58	224.64	224.56	222.6	224.75
38	220.26	221.00	220.45	220.2	220.08
39	216.72	216.72	216.83	216.33	216.45
40	212.09	212.23	213.00	212.59	212.09
41	208.50	208.62	208.13	208.2	207.88
42	204.30	204.46	204.60	204.8	204.54

Table 2 Measurements of Known Overtones (Periods in Seconds)

Mode	Slichter ⁶	Present observations		
		Series 1	Series 2	Series 3
$1S_2$	1,479	1,480.48	1,473.4	1,498.53
$1S_3$	1,060.8	1,059.3	1,066.67	1,059.31
$2S_2$	904.2	902.2	{ 902.3 898.8	903.53
$2S_3$		819.2	819.2	819.2 (weak)
$1S_4$	858.8	847.44	842.8	841.64
$1S_5$	734.4	735.81	734.05	731.43
$2S_4$	724.8	722.82	723.67	
$2S_5$	660.0	660.64	658.20	{ 667.82 660.64
$1S_6$	607.80	605.32	607.72	602.35
$3S_2$	580.2	587.94	588.50	590.77
$1S_8$	557.3	563.67	564.18	563.67
$1S_{10}$	466.6	465.45	465.45	465.45

Table 3 Possible Unknown Overtones (Periods in Seconds)

	Series 1	Series 2	Series 3
1	1,280	1,280	{ 1,304 1,280
2	568.89	570.47	568.88
3	563.67	654.18	563.67
4	546.13	546.13	548.47
5	525.13	525.13	
6	512.00	512.00	512.00
7	495.48	495.88	
8	491.52	491.13	491.52
9	483.78	483.02	480.00
10	467.42	466.5	
11	465.45	465.45	465.45
12	455.11	453.10	455.11
13	420.82	420.53	423.7
14	417.96	417.96	417.96
15	410.97	409.6	
16	408.23	407.97	406.89
17	402.88	401.57	401.57
18	400.26	400.0	
19	396.38	397.67	396.38
20	378.09	378.56	381.60
21	375.78	376.47	374.63
22	362.48	362.48	
23	341.33	340.76	341.33
24	322.50	322.01	323.36
25	312.67	311.72	311.88
26	304.16	304.50	305.67
27	300.44	299.85	301.88
28	294.68	294.25	
29	278.0	278.64	276.78
30	245.76	245.34	
31	243.8	243.20	
32	186.46	186.35	
33	185.34	185.00	185.06

the even harmonics again have greater amplitudes than the odd harmonics. A similar but more dramatic effect was recorded by R. D. Moore *et al.*¹² and can be seen between oS_{22} to oS_{38} in Figs. 3 and 4 of their article. At present, I know of no theoretical reason why more energy should be preferentially coupled to the even harmonics; however, this is an observed fact that may not occur frequently.

(4) The similarity between our own observations and occasionally with those of others as far as the overtones could be identified is also significant. Some of the overtones seem to be close to the fundamental oS_n harmonics.

After a close analysis of the data, it seems that the instrument can detect spheroidal oscillations of the Earth due to earthquakes of magnitudes 7, 6, and 5.5 and possibly more subtle continuous effects such as energy coupled to these modes by the Moon's tide, and so on. In Table 1, the observed data for all three experiments are compared with the recorded data reported by other observers; our results are well within the spread of the data recorded during the Chilean and the Alaskan earthquakes of 1960 and 1964 respectively¹⁵.

In Table 2 are given the observed known overtones, while in Table 3 a number of lines that have been observed on three experiments are reported. Some of these lines are the dominant peaks on the record. Many of these lines are thought to be overtones not so far observed and which cannot at present be identified for lack of theoretical data based on a model of the Earth.

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Doppler Velocity Measurements using White Light

VELOCITY measurements, based on observations of the Doppler shift in frequency of radiation scattered by moving objects, have been made using various optical arrangements (for example, refs. 1-6). The coherency requirements of the illuminating radiation have been considered by Rudd⁵, who concluded that

conventional (that is, not laser) light sources could, in principle, be used. Until recently, however, all proposed optical systems have required such critical alignment or small effective source size (to provide sufficient spatial coherence) that the use of conventional light sources was impractical. Consequently, laser light sources have had to be used exclusively. This is now not necessary and it is demonstrated here that the schlieren-interferometer arrangement proposed by Schwar and Weinberg^{7,8} can be used even with a white light source. To show that Doppler shifts in frequency that are very much smaller than the line width of the illuminating radiation can be detected, the velocity of a slowly moving pendulum bob was measured.

Fig. 1 shows all the details of the optical system. The detector, D, records the beat frequency, v_b , produced by the interference of the two differentially Doppler shifted beams selected by the apertures A_1 and A_2 in the schlieren blind, S. If θ is the angle between the two beams scattered by the same point on the moving object, the observed beat frequency is given by

$$v_b = \frac{u\theta}{\lambda} \quad (1)$$

where u is the velocity of the scattering point perpendicular to the transilluminating beam, and λ is the effective wavelength of the source. It has been shown⁸ that this beat frequency can be interpreted as the intensity oscillations that occur when an interference fringe pattern moves across the front of a point detector. The velocity of these fringes is Mu , where M is the magnification of the test space at the detector, and so v_b is also given by

$$v_b = \frac{uM}{\lambda_i^*} \quad (2)$$

where

$$\lambda_i^* = \frac{\lambda}{M\theta} \quad (3)$$

is the fringe spacing at the recording plane. It follows that u can be determined by measuring M , λ_i^* and v_b .

The positioning of D is achieved by removing S and locating the corresponding image point at which the velocity measurement is required. On replacing S the detector sees a spatially filtered image of the test space. Fig. 2a shows such an image of a suspended droplet. Figs. 2b and c are filtered images of a single straight edge and rod respectively. All were recorded with the optical system at a magnification of 2.64 on Ilford R52 panchromatic plates using a 12 V 50 W tungsten-halogen filament lamp as a light source. Measurements made on the original negatives gave a fringe spacing of 1.050 ± 0.005 mm.

The fringes shown in Fig. 2b are similar to Young's white

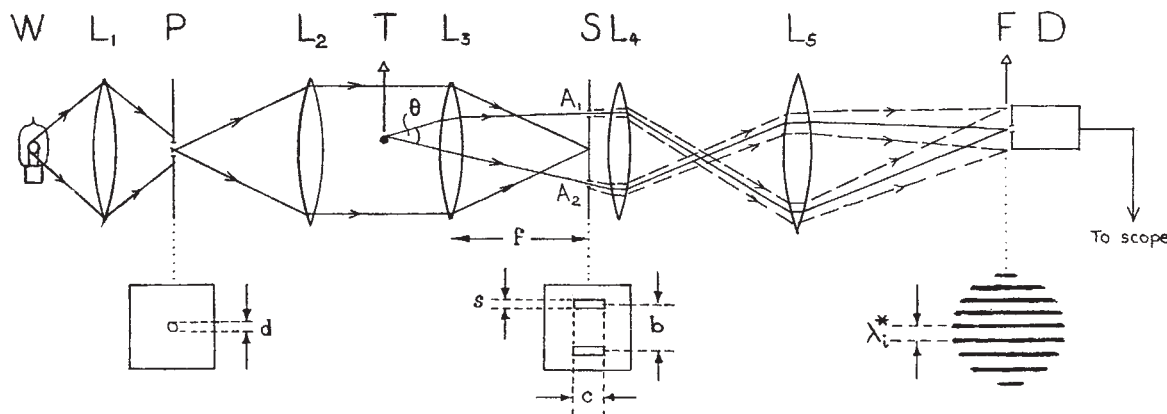


Fig. 1 Schlieren-interferometer optical arrangement. W, 50 W tungsten-halogen lamp; P, screen with pin-hole; T, moving scatterer; S, schlieren blind; A_1 , A_2 , selective apertures; F, spatially filtered image of moving scatterer, that is, moving fringe pattern; D, photodetector; L_1 , condensing lens, focal length 173 cm; L_2 , collimating lens, focal length 173 cm; L_3 , schlieren lens, focal length 173 cm; L_4 , first imaging lens, focal length 50 cm; L_5 , second imaging lens, focal length 10.8 cm; d , 1.00 ± 0.05 mm; s , 0.40 ± 0.05 mm; b , 2.50 ± 0.05 mm; c , 2.20 ± 0.05 mm; λ_i^* , fringe spacing.

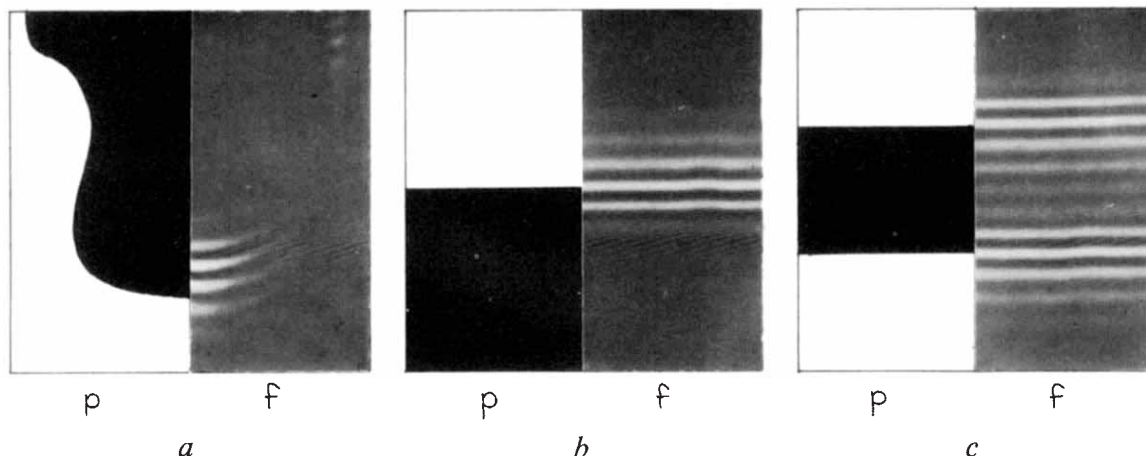


Fig. 2 White light spatially filtered images of various test objects; p, profile of test object; f, filtered image of test object. a, Suspended droplet; b, single straight edge; c, rod.

light interference fringes. The number of fringes, N , arising from a single scattering point is given by

$$N = \frac{2\lambda}{\Delta\lambda} \quad (4)$$

where $\Delta\lambda$ is the effective line width of the source. In the case of an extended scatterer the number of fringes will be greater than this, being determined by the number and separation of the scattering points. Fig. 2c shows, in the case of a 2.2 mm diameter rod, that at least eleven white light interference fringes are formed in its filtered image. It follows that more accurate beat frequency (and hence velocity) measurements can be made on moving extended scatterers than on moving point scatterers. Fig. 3 shows an oscilloscope trace of the white light beat frequency signal produced by an extended scatterer (in the form of three 0.2 mm diameter wires irregularly spaced but roughly parallel to each other) 3 mm wide attached to the bottom of a pendulum moving across the transilluminating beam. In this case, the number of detectable oscillations is ten. The beat frequency was detected with an EMI 9529A photomultiplier, fitted with a 0.2 mm entrance aperture, and the output voltage developed across a 5 k Ω load resistor was displayed on a 547 Tektronix scope fitted with a 1A7A plug in. The H.T. on the photomultiplier was set to 1.55 kV. As the sweep speed was 0.2 s cm⁻¹ the average beat frequency corresponded to 2.85 $\pm$ 0.05 Hz, and so the velocity given by equation (2) was 1.13 $\pm$ 0.03 cm s⁻¹.

The effective wavelength of the light used in this measurement, calculated from equation (3), with θ put equal to b/f (where b is the separation of the selective apertures A_1 and A_2

and f is the focal length of the schlieren lens), corresponded to ~ 5750 Å. Taking N as ~ 6 for a point scatterer the effective line width of the light source, given by equation (4), was ~ 1900 Å (that is, $\sim 1.7 \times 10^{14}$ Hz).

For formation of the maximum possible number of fringes the beam width at the recording plane must be greater than the width of the interference pattern. As the width of the two overlapping beams is determined⁹ by the amount of diffraction caused by the selective apertures A_1 and A_2 , this will occur only if

$$\frac{b}{s} \geq \frac{\lambda}{\Delta\lambda} \quad (5)$$

where s is the width of the selective aperture. But b/s should not be made too large as this will result in an unnecessary reduction in the amount of light falling on the detector. For the system described above $b/s \approx 5$ and $\lambda/\Delta\lambda \approx 3$.

The precision of a Doppler velocity measurement depends ultimately on the number of fringes that pass across the point detector. Ideally, N should be made as large as possible. However, if N is increased by decreasing the effective line width of the source the spatial resolution of the measurement decreases. This is because the distance, w_o , over which the velocity measurement is made is given by⁹

$$w_o = \frac{N\lambda}{\theta} \quad (6)$$

and the depth of focus, l , is

$$l = \pm \frac{N\lambda}{\theta^2} \quad (7)$$

Consequently, if high spatial resolution is required θ must also be made as large as possible. As the intensity of the scattered light generally decreases with increasing θ , its upper limit will eventually be set by the brightness of the light source and sensitivity of the detector. Although it has been demonstrated that a small, 50 W, incandescent filament lamp can be used for Doppler velocity measurements there are, of course, very much brighter thermal sources available. It seems, therefore, that even if a laser light source were unavailable, it should be possible, using, for example, a high pressure xenon or mercury vapour discharge lamp, to carry out precise Doppler velocity measurements of high spatial resolution.

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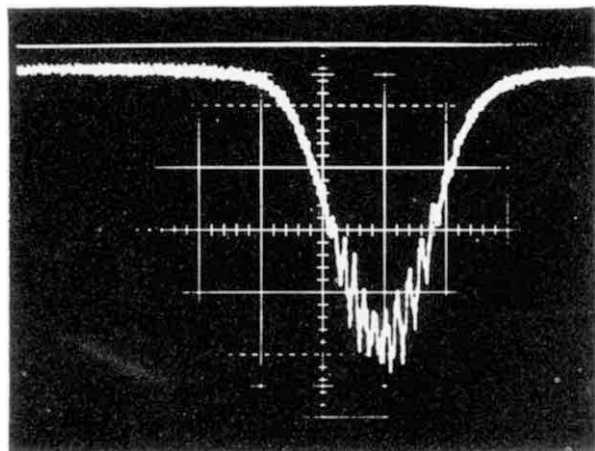


Fig. 3 White light Doppler beat frequency oscillogram trace. Scale 0.2 s cm⁻¹ and 10 mV cm⁻¹.

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Possible Tertiary Age for Some Antarctic Cirques

SOME large cirques cut into the ridges above the Wright Valley, in the McMurdo Oasis, Antarctica ($77^{\circ} 30' S$, $161^{\circ} E$), are now free of ice and are below the permanent snow line (Figs. 1 and 2). Present day precipitation is approximately 100 mm of snow per year; hence it is a desert region into which the Wright Upper Glacier can only intrude 8 km before ablation losses exceed the supply of ice from the polar plateau. The cirques must have been cut during a local glaciation, not a continental one, because, during a rise of the ice of the polar plateau and a spreading of the ice sheet, precipitation in the area would be reduced even below that of the present, and even at times of lower level of the polar plateau there is little likelihood of significantly higher precipitation than at present. The latter conclusion is supported by evidence from the Taylor Valley, 20 km south of the Wright Valley, where that much of the valley has been ice free for at least 2.7 m.y.¹.

The processes responsible for cirque cutting are not fully understood². There are four principal theories of cirque erosion of which three are concerned with glaciers of warm temperate areas: the bergschrund theory³ involves diurnal freezing and thawing at the base of the bergschrund; the meltwater theory^{4,5} stresses the importance of meltwater and rainwater running down the backwall of the cirque, freezing into rock crevices and shattering the rock; the rotational slip theory⁶ involves the sliding of a cirque glacier over its bed and the abrasion by debris included in the sole of the glacier. These theories are all concerned with cirque glaciers which consist of ice the temperatures of which at any depth are at pressure melting-point for that depth, apart from a surface layer of cold ice, up to 20 m or so thick, which is cooled by the atmosphere well below the freezing point in winter. The fourth theory⁷ is concerned with the boundary between cold ice (that is, ice with a temperature well below $0^{\circ} C$ because of its cold environment) frozen to the bedrock, and wet ice close to the pressure melting point. This boundary would oscillate slowly in response to external conditions and freeze-thaw action at the $0^{\circ} C$ boundary would cause shattering of the rock in the cirque

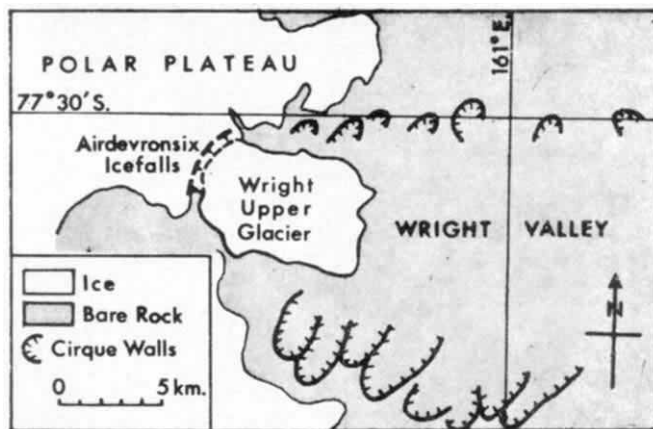


Fig. 2 Location of the ice-free cirques of the upper Wright Valley, Antarctica.

walls and floor. This theory, like the preceding three, is essentially concerned with glaciers in which the dominant processes occur at temperatures around $0^{\circ} C$ and, according to these theories, glaciers composed of colder ice will not provide favourable environments for erosion processes.

The cirque and small valley glaciers of the McMurdo Oasis are composed of ice with a temperature of about $-20^{\circ} C$. Field observations show that at present they are not eroding their beds. Any meltwater draining from them is clear (rock-flour was not observed) and they slide or creep over frozen rock or frozen old moraine which they can neither abrade nor move; hence, contemporary moraines at the sides and snouts of glaciers are composed of debris which has fallen on to the glaciers from cirque or valley walls.

The cirques of the McMurdo Region must have been cut when Antarctica experienced a temperate climate. Assuming that the altitude of the cirque floors (1,600 to 1,800 m) has been constant it would be necessary, in present day climatic conditions, to go at least as far north as latitude $60^{\circ} S$ to find cirque glaciers eroding their basins at similar altitudes. Antarctica has been moving southwards during the Cenozoic⁸; assuming that the McMurdo Region has taken the shortest route southwards and has been moving at a steady rate of 20 cm/yr through 17° of latitude, the cirques would have last been in appropriate latitudes for cirque erosion 9.5 m.y. BP. Because 20 cm/yr is likely to be in excess of the maximum rate of movement and the movement may not have been in a straight line, the resulting Pliocene age for the cirques is an absolute minimum possible age.

Fig. 1 Cirque above the north wall of the Wright Valley, Antarctica.



The best evidence available from palaeomagnetic data suggests that the McMurdo Oasis was last north of the Antarctic Circle at least 50 m.y. BP (ref. 9 and personal communication from D. A. Christoffel). This suggests that the alpine glaciation in which the McMurdo cirques may have been cut could actually be much older than 9.5 m.y. and could well have taken place in early or middle Tertiary times.

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Drag on Clusters of Submicron Spheres in Gravitational and Electrical Fields

THE dependence of hydraulic and aerodynamic drag on particle shape has been of interest for a considerable time but theoretical work has greatly exceeded experimental results, especially for submicron particles. Fuchs¹ gave a concise summary of the position and Preining² and Vomela and Whitby³ have published mainly theoretical articles. Kunkel⁴ determined the drag on various configurations of steel balls glued together and falling in oil, and Megaw and Wiffen⁵ compared the diffusion coefficient of single and clustered submicron polystyrene spheres. Stöber *et al.*⁶ deduced that the Stokes diameter d_n of a cluster containing n spheres should be related to the diameter d_1 of a single sphere by the expression

$$f_n = \frac{d_n}{d_1} \geq n^{\frac{1}{2}}$$

and confirmed its validity in an experiment in which single particles and clusters of submicron polystyrene spheres were

centrifuged out of a spinning air stream. Stöber *et al.* also showed that, when expressed in terms of the Stokes diameter, Kunkel's results (in which the unit sphere was 0.12 cm diameter) agreed very well with those for submicron spheres in air.

The diffusion coefficient D ($\text{cm}^2 \text{s}^{-1}$) and the electrical mobility m ($\text{cm}^2 \text{V}^{-1} \text{s}^{-1}$) of a particle carrying charge e are related by the Einstein equation

$$D = \frac{299.8}{e} k T m$$

k being Boltzmann's constant and T the absolute temperature. For a spherical particle carrying a single electronic charge at 20° C, this reduces to $m = 39.6 D$ and is much used by aerosol physicists. Megaw⁷, pointing out that the diffusion coefficient is dependent on shape, said that it was not known whether the electrical mobility was dependent in the same way, and hence whether the Einstein relationship applied to non-spherical particles. The results given here show that it does not, and that the drag on a cluster of particles depends on whether the particle is moving in a gravitational or an electric field.

Table 1 Ratio, f_n , of Stokes Diameter of Singly Charged Clusters containing n Spheres and moving in an Electric Field to that of a Single Sphere

Unit sphere diameter (cm)	No. of spheres in cluster			
	2 f_2	3 f_3	4 f_4	5 f_5
1×10^{-5}	1.28	1.49		
1.6×10^{-5}	1.35			
2.2×10^{-5}	1.34			
3.3×10^{-5}	1.32	1.57	1.81	2.00
5.0×10^{-5}	1.31	1.58		
7.4×10^{-5}	1.29	1.55	1.79	
7.6×10^{-5}	1.28	1.56		
1.15×10^{-4}	1.29	1.57		

The experiments were performed using the mobility spectrometer described by us^{8,9}. In this the aerosol is introduced as a narrow sheet midway between two parallel plates at equal and opposite potentials. Clean carrier gas flows through the instrument at the same speed as the velocity of introduction of the aerosol. Individual aerosol particles are carried across the gap between the plates and deposited on them at distances from the entrance inversely proportional to the electrical mobilities of the particles. If a monodisperse but coagulated aerosol at charge equilibrium is used, the particles are deposited on the plates in visible bands corresponding to singly, doubly, triply and so on charged singlets, and similarly charged doublets, triplets and so on. Fig. 1 is a photograph of the deposit on a plate, on the centre line of which a number of coated electron microscope grids were fixed before use to enable

Table 2 Comparison of Stokes Diameter Ratio, f_n , for Clusters in Gravitational Fields, Diffusing Clusters and Singly Charged Clusters in Electrical Fields

Diameter of unit sphere (cm)	Values of f_n					
	Glued glass clusters falling in oil ⁴	Magnetized steel clusters falling in glycerol [*]	Polystyrene clusters diffusing in air ⁵	Magnetized steel clusters falling in syrup ⁶	Polystyrene clusters centrifuged from air ⁶	Singly charged clusters in an electric field
No. of spheres in cluster						
2	1.17	1.19	1.18	1.20	1.18	1.31
3	1.28	1.28	1.32	1.34	1.33	1.55
4		1.41		1.46	1.47	1.80
5		1.48	1.52	1.56	1.53	2.00
6	1.54			1.64	1.66	

* Unpublished results of Megaw.

positive identification of the bands to be made. Specimen photographs of the grids are also shown.

Table 3 Calculated Values of Electrical Mobility of Clusters			
Diameter of unit sphere (μm)	No. in cluster	(i) Mobility (cm ² V ⁻¹ s ⁻¹) using Stöber's f_n values	(ii) Mobility (cm ² V ⁻¹ s ⁻¹) using Megaw and Wells's f_n values
0.1	2	1.98×10^{-4}	1.57×10^{-4}
	3	1.64×10^{-4}	1.22×10^{-4}
	4	1.41×10^{-4}	9.69×10^{-5}
	5	1.31×10^{-4}	8.28×10^{-5}
0.5	2	2.02×10^{-5}	1.71×10^{-5}
	3	1.78×10^{-5}	1.42×10^{-5}
	4	1.58×10^{-5}	1.20×10^{-5}
	5	1.50×10^{-5}	1.07×10^{-5}
1.0	2	9.03×10^{-6}	7.90×10^{-6}
	3	7.92×10^{-6}	6.58×10^{-6}
	4	6.93×10^{-6}	5.60×10^{-6}
	5	6.65×10^{-6}	5.00×10^{-6}

(i) Calculated from diffusion coefficient assuming Stöber's f_n values; (ii) as would be obtained by an electrical method assuming Megaw and Wells's f_n values.

By comparing the distances from the entrance at which particular clusters are deposited it is possible to determine the electrical mobility of each configuration and hence the value of its Stokes diameter (the diameter of the spherical particle having the same mobility as the cluster) using the theoretical expression derived by Fuchs and Stechkina¹⁰. The ratios f_2, f_3 and so on can then be determined.

The results for clusters made up of spheres of diameter 1×10^{-5} to 1.15×10^{-4} cm are given in Table 1. In Table 2 the values of f_n obtained by Kunkel⁴ for glued clusters of glass spheres falling in oil, Megaw (unpublished work) for magnetized steel clusters falling in glycerol; Megaw and Wiffen⁵ for submicron clusters of polystyrene spheres diffusing in air, Stöber *et al.*⁶ for magnetized steel spheres falling in syrup and for micron sized clusters of polystyrene spheres centrifuged from air, are compared with the results of work described here. The f_n values for the electrically charged spheres differ considerably from the results for the other methods, which are in close agreement.

Megaw has noticed (unpublished work) that when asymmetric clusters of spheres are falling in a liquid the cluster takes up one of several preferred orientations. For example, doublets rarely fall in a vertical or horizontal mode but usually with the common axis inclined at about 60° to the vertical, and doublets which are released in the liquid in the vertical or

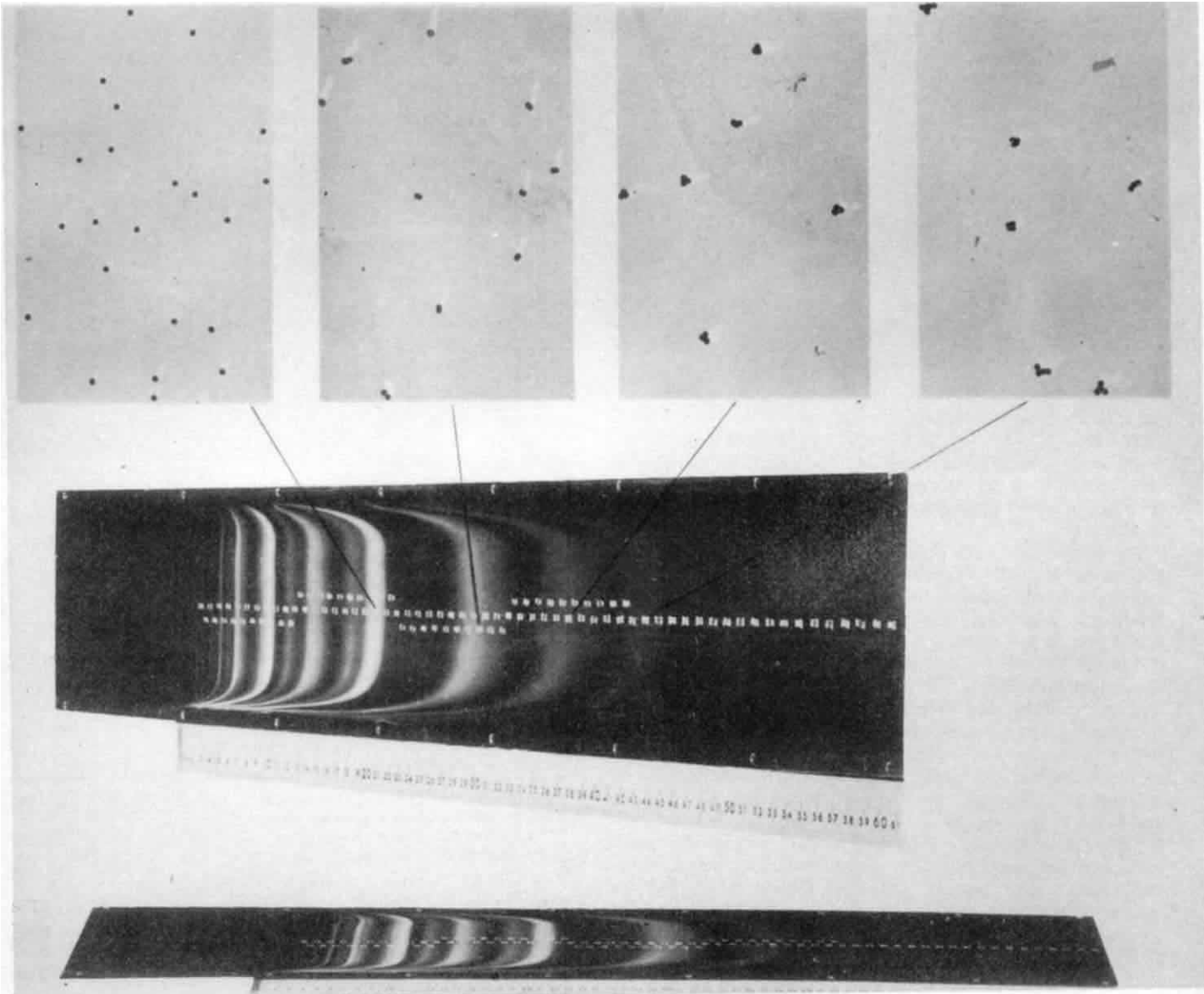


Fig. 1 Deposition bands of clusters of 0.33 μm diameter polystyrene spheres with identification electron micrographs.

materials in Table 1b can be traced back chiefly to the fluoride electrode and can be attributed to a marked difference in ionic strength between the unbuffered standard sodium fluoride solutions and the fluoride ion in the distillate from pyrohydrolysis. The higher ionic strength of the latter will tend to decrease the fluoride ion activity¹⁵. The opposite trend in the case of compound 12, which may indicate that some species in the distillate from teeth tend to interfere with the Belcher method, is being investigated further.

Samples of Darjeeling tea were subjected to decomposition by pyrohydrolysis (total fluorine) and also to low temperature ashing at 100–150° C followed by pyrohydrolysis (inorganic fluorine) in an attempt to distinguish between the two types of fluorine^{3–6}. The low temperature ash (Tracerlab) allows the complete removal of organic matter because electro-magnetically excited oxygen leaves the inorganic constituent undestroyed. The almost identical results for compound 7 (i) and (ii) indicate the absence of organic fluorine in tea, in agreement with Peters⁷.

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BIOLOGICAL SCIENCES

Neutralization of Murine Mammary Tumour Virus by Sera of Women with Breast Cancer

MOUSE mammary tumour virus (MTV) causes breast cancer in mice. The mouse-MTV system is a useful model in the search for the hypothetical human mammary tumour virus (HMTV) causing the parallel disease in women. B particles similar in

morphology to MTV were observed in negatively stained preparations of human milk by Moore *et al.*¹, and there seemed to be a connexion between the appearance of particles in the milk and the incidence of breast cancer among women.

It therefore seemed reasonable to explore the possibility of a close antigenic relationship between MTV and HMTV by means of cross-neutralization studies. Instances of such cross-antigenic relationships between viruses causing similar diseases in different species are known to exist. The familiar existence of smallpox-cowpox is a case in point. Human measles, canine distemper and bovine rinderpest form one of the several sub-groups of myxoviruses in which various degrees of cross-neutralization have been demonstrated². Similar cross-neutralization has been shown with the herpesviruses *H. hominis* (herpes simplex) and *H. simiae* (monkey B virus)³. Fink *et al.*⁴ have reported data that suggest a degree of neutralization of a murine leukaemia virus (Rauscher) by sera of leukaemic patients. Data indicating the ability of sera from breast cancer patients to neutralize MTV are reported here.

In a preliminary experiment, MTV was neutralized by heterologous hyperimmune rabbit serum. Skim milk from the MTV-positive RIII mouse strain, containing approximately 10^5 ID₅₀/0.1 ml. at a dilution of 1:100, was incubated for 1 h at 37° C with ten-fold dilutions of antiserum. The preparation of the antiserum has been described already⁵. The virus-antiserum mixtures (0.1 ml.) were inoculated into C57BL mice and the infective status of the mice was determined by detection of viral antigen in the milk at the third lactation by the immunodiffusion assay of Charney *et al.*⁵. The presence of viral antigen in the milk at the third lactation is indicative of tumorigenesis^{5,6}. The results obtained are summarized in Table 1. As expected, antigen detection in third lactation milk was eventually followed by tumorigenesis. Neutralization of the virus by the hyperimmune rabbit antiserum was substantially complete only at the highest antiserum level used (1:10 dilution).

As a result of the weak neutralizing capacity of the supposedly hyperimmune rabbit serum, modifications were made in the neutralization tests with human sera. Since RIII mouse milk contains much soluble (non-virion) viral antigen which might possibly interfere with the neutralization test, the MTV virions were purified by density gradient centrifugation by the method of Lyons and Moore⁷. The purified virion fraction, stored at -90° C until use, contained approximately 10^4 ID₅₀/0.1 ml. Then 0.2 ml. of the purified MTV preparation was mixed with 1.8 ml. of serum, incubated for 1 h at 37° C and permitted to stand for 18 h at 4° C before inoculation of 0.1 ml. amounts into C57BL mice. The virus therefore contained approximately 100 ID₅₀/0.1 ml. at final dilution and the sera were practically undiluted. The five control sera from young adults were selected at random from the serum bank of the Philadelphia Department of Health. The description of these sera and the results obtained, as determined by the MTV assay, are given in Table 2. The mean incidence of MTV infection in mice inoculated with the control serum-virus mixtures was 87%, which is the usual incidence of antigen in third lactation milks of mice given fully infective doses of MTV⁵. The infectivity of the tumour sera-virus mixtures (mean = 69%) was lower in every case than those of the controls.

These data were analysed statistically. The difference between the control and tumour groups was significant ($P = 0.02$). Two of the tumour sera (H.G. and B.W.) were both significantly different from the control group ($P = 0.02$) and a third (C.S.) was just short of significance ($P = 0.057$). The 95% confidence intervals of the control and tumour groups barely interlock (control sera, 78.8%–95.4%; tumour sera, 57.9%–80.8%).

The presence of neutralizing antibodies in sera from human breast cancer patients and their absence from normal human sera indicates a viral aetiology for the human disease. It also indicates that the human and the murine viruses are closely related. Our results support the electron microscopic findings

Table 1 Neutralization of MTV by Heterologous (Rabbit) Anti-MTV Serum

Antiserum dilution	Infected mice* Mice tested	% mice infected	Mice with tumours† Mice tested	% mice with tumours
10 ⁻¹	1/15	7	1/14	7
10 ⁻²	10/15	67	9/15	60
10 ⁻³	8/15	53	8/15	53
10 ⁻⁴	11/15	73	12/15	80
10 ⁻⁵	11/14	79	10/12	83
10 ⁻⁶	11/14	79	10/14	71
Control (no antiserum)	10/12	83	6/11	55

* Determined by MTV assay⁵ at third lactation.

† Mice observed for 18 months.

Table 2 Neutralization of Purified MTV by Sera from Women with Breast Cancer compared with Normal Controls

Serum	Interval to treatment *	Interval to serum †	Patient treatment	Age (yr)	MTV neutralization‡	
					Mice infected Mice tested	% mice infected
C.S.	1 yr	8 yr	r.m., r-t.	85	9/13	79
E.M.W.	1 month	2 yr	r.m.	60	7/10	70
H.G.	3 months	5 yr	Excision	76	9/14	64
B.W.	1 yr	4 months	r-t.	36	9/14	64
M.B.G.	3 weeks	5 yr	r.m.	55	9/11	82
			Breast cancer sera, totals		43/62	69.3
A.B.	Normal serum control				10/12	83
J.L.	"				11/12	92
S.M.	"				12/14	86
B.G.	"				14/16	88
J.S.	"				7/8	88
			Control sera, totals		54/62	87.0

r.m., radical mastectomy; r-t., radiotherapy.

* Duration of symptoms before medical treatment.

† Interval from time of treatment to time serum was drawn.

‡ Determined by MTV assay⁵.

of Moore *et al.*¹ of B particles in human milk which are morphologically identical with mouse MTV.

Further neutralization studies of human breast cancer sera obtained from patients at various stages of the disease are being done using control non-tumour sera and tumour sera from patients with tumours other than breast cancer paired for age and sex.

The cross-antigenic relationship between MTV and HMTV indicated in this study suggests that MTV could be used to render women immune to breast cancer. This would require that antisera to MTV and HMTV be reciprocally cross-neutralizing, that is, antibody to MTV must also neutralize HMTV. Experimental techniques to demonstrate this do not exist at present.

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Localizing ³H-GABA in Nerve Terminals of Rat Cerebral Cortex by Electron Microscopic Autoradiography

CONSIDERABLE biochemical, physiological and pharmacological evidence supports the idea that GABA is an important inhibitory neurotransmitter substance in the mammalian central nervous system (CNS)¹⁻³. Cytochemical techniques for demonstrating the cellular location of this amino-acid in the CNS have so far not been available.

Slices and synaptosomes from rat cerebral cortex will actively accumulate ³H-GABA when incubated *in vitro*⁴. After briefly incubating with ³H-GABA, the unchanged amino-acid is concentrated in the tissue without any significant accumulation of labelled metabolites. Furthermore, the radioactive GABA can be released by electrical stimulation from cortical slices⁵, and it has a subcellular distribution closely similar to that of the endogenous amino acid⁶. This labelling technique, in combination with autoradiographic procedures, therefore offers a potential method for the localization of GABA-containing structures in the CNS. Such an approach

has recently been applied to the localization of ^3H -GABA at the light microscope level in slices of rat cerebellar cortex⁷ and rabbit retina⁸. We now present preliminary results obtained by electron microscope autoradiography which indicate that ^3H -GABA is predominantly accumulated by nerve terminals in rat cerebral cortex.

Small slices of rat cortex were incubated with ^3H -GABA as previously described⁴. The concentration of ^3H -GABA in the incubation medium was 5 μM (10 $\mu\text{Ci}/\text{ml}$; 2,3- ^3H -GABA, specific activity 2.0 Ci/mmol, New England Nuclear Corp.) and the incubations were performed at 25° C for 10–30 min. Some experiments were also performed with samples of rat cortex homogenates prepared in isotonic sucrose, and incubated in Krebs phosphate solution with labelled GABA as we have described. At the end of the incubation with ^3H -GABA, the labelled medium was discarded (after centrifugation of homogenate samples), and the tissue slices or homogenate pellets were washed with ice-cold medium, and then fixed by the addition of fresh medium containing glutaraldehyde. In preliminary experiments, using these uptake conditions, tissue extracts were subjected to ion exchange chromatography or paper chromatography⁴. ^3H -GABA accounted for $95 \pm 9\%$ of the total radioactivity in both slices and homogenate pellets (mean $\pm$ s.e.m. of three experiments), and ^3H -GABA was the only labelled compound detected by paper chromatography. We have also determined the extent of retention of ^3H -GABA in the tissue samples after fixation, by dissolving tissue samples and determining their radioactivity after various fixation procedures. These results (Table 1) indicate that almost two thirds of the labelled GABA was retained after fixation with glutaraldehyde. For autoradiographic studies, the fixed samples were treated with osmium tetroxide, dehydrated in ethanol and embedded in epoxy resin.

Table 1 Effect of Fixation Conditions on Retention of ^3H -GABA

Fixative	% retention of ^3H -GABA
3% potassium permanganate	17.8 (n=2)
5% glutaraldehyde	65.2 ± 4.1 (n=4) ($\pm$ s.e.m.)

Cortical homogenates were incubated with ^3H -GABA as described in the text; at the end of the incubation, the homogenate was centrifuged, and the radioactivity present in the pellet was determined after solubilization overnight with NCS solubilizer (Searle). Fixatives were added to other labelled pellets obtained from the same homogenate, and after standing for 40 min at 4° C the fixative solution was removed, the pellets rinsed and solubilized for counting. All fixative solutions were made up in the incubation medium (Krebs phosphate solution). Results are expressed as percentages of the amount of ^3H -GABA present in unfixed samples, and are mean values of n experiments.

Autoradiographs were first prepared using tissue sections of 1–2 μm thickness, in order to evaluate the overall distribution of radioactivity. The samples were dipped in Ilford L-4 emulsion and developed with DK 170 developer (Kodak) after exposure periods of 5–15 days. Examination by light microscopy showed intense autoradiographic activity over the cortical slices and homogenate pellets. In cortical slices the radioactivity was restricted to the neuropil, with a notable absence of silver grains over the cell bodies of the large cortical neurones. There was no obvious localization of ^3H -GABA within the layers of the cortex. We have now used very small slices prepared with a mechanical chopper, so that the conditions of the autoradiographic study are very similar to those used in previous biochemical studies^{4,6}. It seems likely that slices prepared in this way are not the most suitable for determining the cytological localization of ^3H -GABA by light microscopy. Our primary objective, however, was to determine the cellular location of ^3H -GABA uptake sites at high resolution by electron microscopy, rather than to examine the morphological distribution of such uptake sites in the tissue.

For electron microscope autoradiography, thin sections (80–100 nm) of the same tissue blocks were placed on celloidin

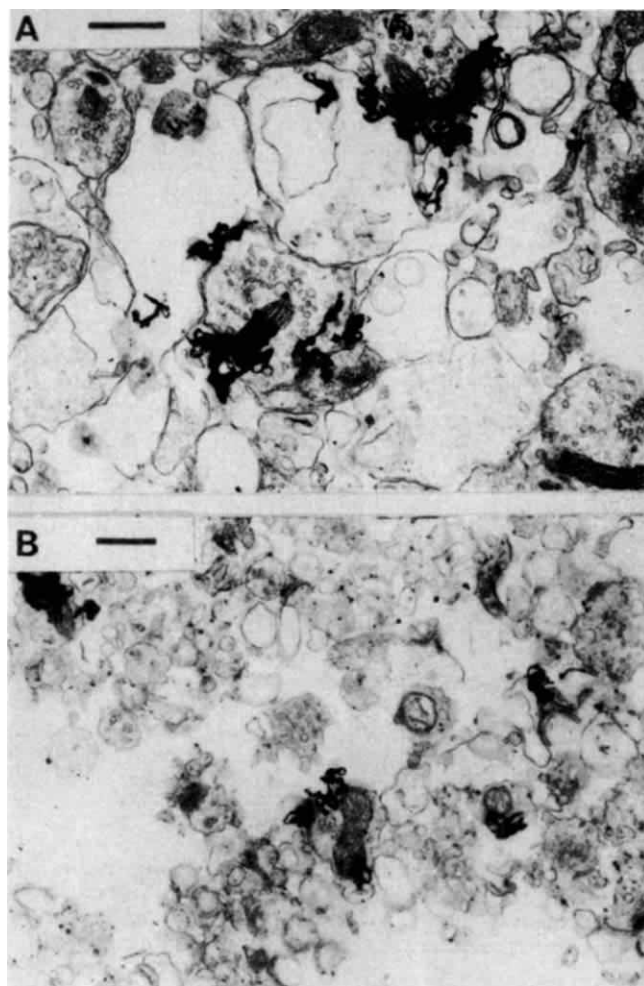


Fig. 1 Electron microscope autoradiographs of tissue samples incubated in ^3H -GABA as described in the text. Regardless of whether the tissue samples were slices (A) or homogenates (B), the predominant site of autoradiographic activity as indicated by the presence of irregular, electron-dense silver coils was over nerve terminals. Clusters of 8–10 grains as seen over the nerve terminals in A were never seen over any other structural element except nerve terminals. The calibration bar represents 0.5 μm .

coated slides, stained with lead citrate and lightly coated by carbon evaporation before dipping in dilute Ilford L-4 emulsion to obtain a monolayer of silver halide crystals. After exposures of 9–21 days, development in D 19B (Kodak) revealed autoradiographic activity over nerve terminals in both cortical slices and homogenates (Fig. 1). The distribution of silver grains was quantitatively analysed in randomly oriented low magnification micrographs of cortical slices. The results (Table 2) showed a highly significant localization of the radioactive GABA to nerve terminals and preterminal unmyelinated axons. These tissue components accounted for an average of $38 \pm 3\%$ of total section area (5 samples of 275 μm^2), but contained $82 \pm 1\%$ of all silver grains in the same sections. In sections of the pellets obtained after the labelling of cortical homogenates with ^3H -GABA *in vitro*, there was again an almost exclusive localization of autoradiographic activity in nerve terminals, with little or no labelling of other components such as free mitochondria or myelin fragments (Fig. 1).

We have estimated the proportion of nerve terminals which contained ^3H -GABA in cortical slices and homogenates. These results (Table 3) show a remarkable agreement between the estimates obtained in slices and homogenates after various periods of autoradiographic exposure. There was no significant difference between the proportion of labelled terminals after various exposure times, which suggests that all labelled

Table 2 Localization of ^3H -GABA in Slices of Rat Cerebral Cortex

Tissue component	Mean percentage of surface area occupied*	Mean percentage of total silver grains†
Glial cells	13.0 ± 1.1	2.1 ± 0.1
Neurone cell bodies + dendrites	38.9 ± 3.0	11.3 ± 1.8
Nerve terminals	23.5 ± 3.6	70.7 ± 2.3
Myelinated axons	5.0 ± 1.7	1.0 ± 0.05
Unmyelinated axons	14.5 ± 1.3	11.2 ± 1.5
Unidentified and extracellular space	5.3 ± 1.1	3.2 ± 1.1

* Percentage of total area occupied by various tissue components was estimated by application of a 220 point grid to randomly selected low power electron micrographs of cortical tissue. The area of tissue in each micrograph was $275 \mu\text{m}^2$, and the results are means $\pm$ s.e. for five analyses.

† The distribution of silver grains was analysed in the same electron micrographs; results are expressed as the mean percentages ($\pm$ s.e.) of total grain population in each micrograph located over the various tissue components.

terminals were estimated even after relatively short exposure times. The only difference observed between exposure times of 9, 15, and 21 days was that the number of silver grains over each nerve terminal increased with the longer exposures. After the 21 day exposure, the median number of silver grains over each labelled terminal in cortical slices was two, with some large terminals giving rise to as many as eight to ten grains.

Table 3 Percentage of Nerve Terminals containing ^3H -GABA in Slices and Homogenates of Rat Cerebral Cortex

Sample and exposure time (days)	Mean percentage of labelled terminals $\pm$ s.e.m.	Total No. of terminals analysed	No. of micrographs analysed
Cortical slices:			
9	27.0 ± 2.4	556	12
15	26.6 ± 1.3	232	5
21	27.2 ± 3.0	679	13
Cortical homogenates:			
9	22.0 ± 2.1	218	7
15	28.4 ± 2.9	214	7
21	29.6 ± 2.3	242	7

Mean results for analyses of five to thirteen autoradiographs of cortical slices or homogenates, each containing forty to fifty nerve terminals.

The similarity between the estimates obtained from cortical slices (27% labelled terminals) and homogenates (28–30% labelled terminals) also suggests that the incubation of small cortical slices *in vitro* leads to an adequate labelling of all the GABA uptake sites. If one assumes that GABA uptake sites are associated with the nerve terminals which contain endogenous GABA, then our results suggest that such terminals account for about 30% of all synaptic terminals in the rat cerebral cortex. This conclusion is in accord with other evidence which suggests that GABA is the principal inhibitory neurotransmitter in the mammalian cerebral cortex^{1–3}.

These preliminary findings indicate that the use of radioactively labelled GABA in conjunction with electron microscope autoradiography will be useful for future studies of the distribution and fine structure of GABA-containing elements in the CNS. Autoradiographic studies at the light microscope level have already provided information on the distribution of such structures in the cerebellum and retina^{7,8}. The analysis of labelled nerve terminals in brain homogenates may make it possible to arrive at an accurate estimate of the relative abundance of GABA terminals in various regions of the brain and spinal cord. The technique may also be applicable to other amino-acids for which a transmitter role has been

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Preparation of Highly Radioactive Bovine Anti-mouse Lymphocyte Antibody

FOR use in humans the active components of anti-lymphocytic serum (ALS) must be sufficiently free of irrelevant substances, concentrated and non-toxic for it to be injected intravenously. With this in mind earlier investigations designed in the context of an experimental model¹ were aimed at (1) preparing pure anti-lymphocytic antibody (ALSAb) from anti-lymphocytic globulin preparations (ALG) and (2) increasing the biological activity of such preparations by labelling the protein in them with a low energy gamma-emitting isotope (^{125}I). It was hoped that the specifically localized irradiation would play a role in incapacitating the target lymphocytes¹. ALS raised in rabbits is widely used, but many workers have reported considerable variation in the quality of ALS from individual rabbits. It would therefore be advantageous to raise ALS in larger animals such as cattle or pigs so that larger pools of material could be obtained. The earlier experiments with ALSAb prepared from rabbit ALS have been extended in the experiments described here, in which the effectiveness of purified bovine anti-mouse lymphocyte antibody (BALSAb) and ^{125}I -BALSAb has been measured. A preliminary investigation has also been made of the possibility of using a column of thymocytes bound to 'Sepharose', for the preparation of BALSAb.

The ALS was raised by injecting a 2 month old Jersey calf in several sites with Freund's complete adjuvant containing 4×10^{10} heat treated thymocytes (49°C , 20 min). A second injection of 3×10^{10} cells, not in adjuvant, was given after 14 days and the calf was bled a week later². The median survival time (MST) of this serum, measured by the standard method used in this laboratory³, was 27 days. Anti-lymphocyte globulins (ALG) were prepared from ALS by precipitation in half-saturated ammonium sulphate (4°C), followed by ion-exchange chromatography (Whatman DE 32) using 0.02 M Sorensen phosphate buffer containing 0.02 M NaCl. ALSAb was prepared from ALG by a batch procedure using one of the methods described previously⁴. Briefly, washed thymus cells in Gey's solution were fixed for 3–4 min in 0.125% glutaraldehyde. After washing, the cells were incubated with normal bovine gamma globulin and then washed by suspending them in 0.1 M acetic acid (pH 3.1) followed immediately by centrifugation (5 min at 600g). After rapid adjustment of the pH to 7 the cells were washed three times in Gey's solution containing 0.1% bovine serum albumin. These "precycled" cells were then used for the batch preparation of ALSAb by adding 1 μg

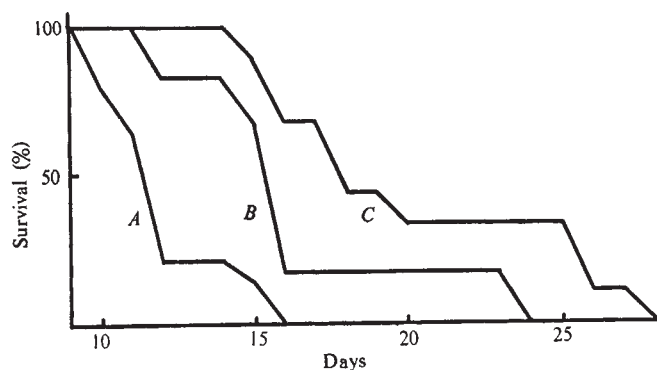


Fig. 1 The survival of A strain tail skin grafted onto CBA male mice. *A* is a group of fourteen untreated controls; *B* is a group of seven mice injected intravenously with 250 µg BALSAb 4 h after grafting; *C* is similar to *B* except that the BALSAb was labelled with ^{125}I (3.2 µCi/µg), and there were ten mice in the group. The horizontal axis is days after grafting.

ALG for every 1×10^6 cells, incubating them at 20° C for 10–15 min, washing three times with Gey's solution, eluting antibody with acid (pH 3.1), rapidly adjusting the pH of both eluate and cells to 7, followed by three more washes of the cells before the start of the next cycle. Up to ten elution cycles can be completed before a significant drop in the yield of ALSAb results. Each eluate was concentrated using 'Aquacide' (Calbiochem) and cytotoxic titres were then measured using ^{51}Cr -labelled lymphocytes by the method of Ruszkiewicz⁴. The eluates were pooled after it was found that they all had specific activities at least ten-fold greater than the starting material. The pool of eluted material was tested for all components of bovine serum by immunoelectrophoresis. Only globulins with a γ_2 mobility were detected in the BALSAb preparation. BALSAb was labelled with ^{125}I by the chloramine-T method⁵ using radioisotope 5 supplied by the Radiochemical Centre, Amersham (IMS 3).

Three groups of male CBA mice aged 3–4 months were grafted with A strain tail skin⁴. Four hours later two groups were injected intravenously with either 250 µg of BALSAb or 250 µg of ^{125}I -BALSAb (3.2 µCi/µg). Fig. 1 shows that unlabelled BALSAb prolongs the life of test skin grafts and that the labelled material shows a somewhat greater prolongation effect than the unlabelled material, confirming earlier results with rabbit ALSAb¹.

In an attempt to develop an easier procedure for preparing ALSAb than the "batch" method, a column of fixed thymocytes

conjugated to 'Sepharose' was prepared. About 10^{10} thymocytes (outbred mouse) were fixed as described earlier and suspended in borate buffer (0.01 M boric acid, 0.025 M Na borate, 0.075 M NaCl, pH 8.4). 'Sepharose 2B' (400 µg, Pharmacia) was prepared for conjugation as described by Porath *et al.*⁶, except that the protein used in their procedure was replaced by fixed thymocytes. The acid wash before use of the 'Sepharose' conjugate as an immunoadsorbent was made on the column after adding 25 mg of normal bovine gamma globulin. For the preparation of BALSAb 10 mg of ALG was added to the column which was then washed with borate buffer until there was no detectable protein in the effluent. The acid elution step was made by passing 0.25 M acetic acid through the column. The absorbance of the effluent was monitored by an LKB Uvicord (240 nm) and the pH was monitored with indicator papers. Two different fractions were obtained, one with the pH of the effluent steady at 3 and the other after borate buffer had been reapplied to the column and at a time when the pH of the effluent was rising (Fig. 2). Table 1 shows that there is no difference in the specific activity of the two fractions, and moreover that the specific activity of these BALSAb fractions is about ten-fold greater than acid-treated starting material (BALG-acid). BALSAb eluted from the column was exposed to similar degrees of acidity and temperature for about 30 min. Table 1 also shows clearly that the untreated starting material (BALG-control) has a cytotoxic titre eight-fold higher than the BALG-acid (15 min at pH 3.1–3.0, 20° C). The relatively greater success of the batch method may well be due to the short time during which the antibody is kept at pH 3. A certain amount of denaturation of antibody by acid may be an explanation of the significant content of IgG without antibody activity, observed previously¹ in ALSAb prepared by the batch method. Denaturation of anti-peptide antibodies kept for 1 h in similar conditions of acidity has been reported⁷. Bachvaroff *et al.*⁸ successfully prepared a purified cytotoxic antibody against thymocytes using a batch method, but they did not include any data on the stability of this antibody in acid conditions (pH 2.5, 0° C, HCl-glycine buffer). Others have noted the lability of ALS in acid conditions^{9,10}, and Woodruff and his colleagues have shown that acid-treated ALG loses its ability to prolong survival of skin allografts¹¹.

It seems reasonable to conclude that the ability of bovine ALS antibody to prolong skin grafts can be increased by labelling the material with ^{125}I . The practicality of preparing BALSAb using a column of insoluble immunoadsorbent seems to be limited at the moment by the marked lability of ALS antibody in acid conditions.

Table 1 Cytotoxic Activity of ALS Antibody eluted from a Column of Thymocyte-'Sepharose' Conjugate

Material	Cytotoxic end point (µg of protein)	Relative cytotoxic titre	Yield (µg)	Relative cytotoxic activity as a factor of:	
				BALG-acid	BALG-control
BALSAb-A	0.34	8.4	285	9.3	1.1
BALSAb-B	0.30	9.8	500	10.9	1.3
BALG-acid treatment	3.1	0.9	—	—	0.12
BALG-control	0.38	7.7	—	8.2	—
Standard (see ref. 1)	2.9	1.0	—	—	—
BALSAb from batch preparation	0.05	58.0	—	—	—

Total yield of gamma globulin (OD₂₈₀) in the BALSAb cuts is about 0.8 mg from 30 mg BALG (2.6%). The yield for batch preparations ranged from 2.5–3.5%.

Relative cytotoxic titre =
 µg standard needed to lyse 50% of target cells
 µg experimental sample needed to lyse 50% of target cells

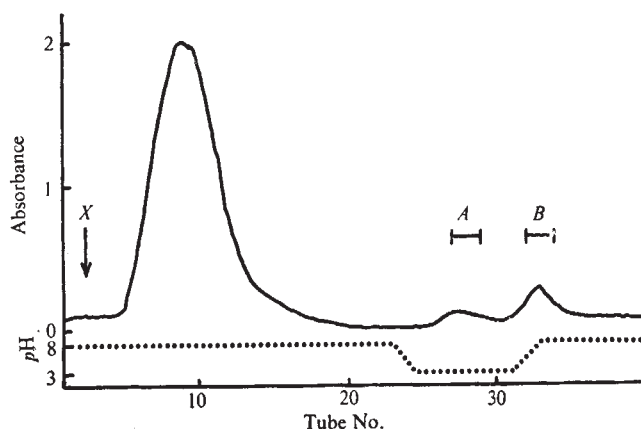


Fig. 2 The effluent from a column (2 cm diameter $\times$ 5 cm) of 400 mg 'Sepharose'/ 10^{10} thymocytes to which 10 mg of bovine ALG had been added at *X* monitored by an LKB Uvicord at 240 nm. The column was washed with borate buffer and acid elution was with 0.25 M acetic acid. Seven ml. fractions were made at a rate of 12–14/h. The dotted line indicates the pH of the effluent. See Table 1 for further information about cuts *A* and *B*.

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***In vitro* Assay of Cell Mediated Immunity in Human Cancer: Definition of Leukocyte Migration Inhibitory Factor**

SEVERAL studies have implicated the delayed hypersensitivity reaction in the body's response to cancer. Hughes and Lytton found that one cancer patient in four demonstrated a delayed cutaneous hypersensitivity response to an antigen consisting of small cytoplasmic particles obtained after ultrasonic disruption of their tumours¹. There have been several studies of the ability of cancer patients to react to the antigens commonly used for delayed cutaneous hypersensitivity testing²⁻⁹; in general, while responsiveness was affected little, if at all, in patients with early cancer, it decreased as disease and debility progressed. The ability to develop contact sensitivity to dinitrochloro-benzene or dinitrofluoro-benzene is decreased in cancer patients, particularly those with advanced disease^{10,11}. Such sensitivity has been shown to be related to prognosis¹².

George and Vaughan proposed the use of *in vitro* cell migration to study delayed hypersensitivity¹³, and the mechanism was further defined by Bloom and Bennett¹⁴. They noted that interaction between lymphocytes from tuberculin-hypersensitive guinea-pigs and *p*-phenylenediamine (PPD) resulted in the formation of a substance which inhibited migration of normal peritoneal-exudate cells. Søberg and Bendixen^{15,16} showed that the brucella antigen inhibited migration of leukocytes obtained from individuals with positive skin tests only. Falk *et al.*¹⁷ sensitized volunteers with homologous skin grafts after which migration of the sensitized lymphocytes was inhibited by antigens from the skin graft donor.

It seemed from these studies that human tumours might either contain or produce a substance which inhibits migration of the patient's lymphocytes. If this substance were the migration inhibitory component of the hypersensitivity reaction, its demonstration by this test would also imply prior sensitization of the peripheral leukocytes.

Human tumour and normal tissue were either minced with scissors and incubated in Eagle's medium (containing 100,000 U of penicillin G, 400 U of streptomycin and 50 mg each of

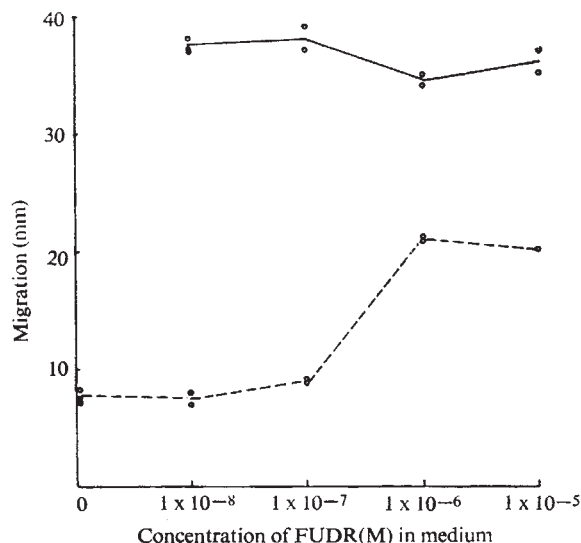


Fig. 1 Effect of 5-fluorodeoxyuridine (FUDR) in partially reversing inhibition of leukocyte migration produced by phytohaemagglutinin. ○—○, FUDR; ○— — ○, FUDR + phytohaemagglutinin.

oxytetracycline and chlortetracycline/l.) for 24 h or disintegrated with ultrasound. The larger cell fragments were cleared from the medium by centrifugation for 10 min at 2,000g. When tests were run to ascertain the effect of continued presence of tumour on leukocyte migration, samples of media were removed before centrifugation. Leukocytes were obtained from blood drawn in heparinized syringes, the erythrocytes were allowed to settle out, and the plasma and leukocytes were transferred to centrifuge tubes. Plasma was removed by centrifugation at 750g for 4 min, and the leukocytes were washed three times with 5% dextrose lactated Ringer and resuspended in an equal volume of Eagle's medium. Ten-lambda siliconized capillary tubes (Drummond) were filled with the suspension, sealed with 'Permoplast' clay, and centrifuged to separate the cells and medium. Finally, the capillary tubes were broken at the leukocyte medium interface before incubation. Stained smears of the leukocytes so prepared revealed about 60% lymphocytes, 40% polymorphonuclear leukocytes, and a few erythrocytes.

The solution derived from the tumour was drawn to fill the tips of siliconized Pasteur pipettes, and the portion of the capillary tube containing leukocytes was inserted into the tip of the Pasteur pipette. The tip of the Pasteur pipette containing the "antigen" solution and the leukocytes in the capillary tube was sealed with Permoplast clay and broken off. The open end was sealed with Dow Corning stopcock grease, and the distance of leukocyte migration along the pipette was determined after 24 h incubation at 37° C.

Most of the tumours liberated into the medium a substance which inhibited migration of the patient's leukocytes (Table 1). Inhibition of migration was no greater with continued presence of tumour cells in the medium than when the cells had been removed before testing for migration. Migration was also inhibited by ultrasonicates of the tumour. Medium which inhibited migration of a patient's leukocytes had no effect on normal leukocyte migration (Table 2). It was possible to distinguish between inhibition of migration resulting from blastogenesis and that resulting from specific migration inhibitory factors by adding 5-fluorodeoxyuridine to the medium at the time of the test. When phytohaemagglutinin (0.04 ml./ml. of medium) was present in the medium, migration did not occur. Partial reversal of this inhibition occurred when blastogenesis was blocked by 5-fluorodeoxyuridine in concentrations greater than 1×10^{-7} M (Fig. 1). Although the inhibition of migration caused by phytohaemagglutinin

Table 1 Inhibition of Autologous Leukocyte Migration by Cancer

Patient	State of tumour preparation	% inhibition of migration control-tumour control × 100	Significance of difference of migration tumour versus control (<i>P</i>)	Tumour specimen
1	Cell free	48	<0.01	Breast carcinoma
2	Cells	41	<0.01	Breast carcinoma
	Cell free	24	0.05	
3	Cells	38	<0.01	Breast carcinoma
	Cell free	28	<0.50, >0.10	
4	Cell free	23	<0.01	Breast carcinoma
	Cell free + FUDR	14	<0.01	
5	Cell free	15	<0.10, >0.05	Breast carcinoma
	Ultrasonic	22	<0.02, >0.01	
6	Cells	79	<0.01	Bronchogenic carcinoma
7	Cells	8	>0.50	Bronchogenic carcinoma
	Cell free	19	<0.05, >0.02	
8	Cells	9	>0.50	Bronchogenic carcinoma
	Cell free	25	<0.10, >0.05	In hilar lymph node
9	Cells	44	<0.01	Carcinoma of maxillary sinus
	Cell free	63	<0.01	
10	Cells	6	>0.50	Colon carcinoma
	Cell free	21	<0.50, >0.10	
11	Cell free	(12)	<0.50, >0.10	Colon carcinoma
	Ultrasonic	17	<0.01	
12	Cell free	33	<0.01	Gastric carcinoma
	Cell free + FUDR	39	<0.01	
13	Cell free	26	<0.02, >0.01	Ovarian carcinoma
14	Cells	36	<0.01	Rectal carcinoma,
	Cell free	15	<0.50, >0.10	Perineal recurrence
15	Cell free	62	<0.01	Squamous of parotid
	Cell free + FUDR	58	<0.01	
16	Cell free	28	<0.01	Thyroid carcinoma

Inhibition of leukocyte migration produced *in vitro* by elements of autologous tumour. Tumour was presented to the leukocytes in Eagle's medium in one of three forms: as the supernatant present after incubation of a tumour mince for 24 h, as the same preparation from which the cells had been removed by centrifugation, or as the ultrasonicate of the tumour. These are denoted in Table 1 as cells, cell free and ultrasonic, respectively. 5-Fluorodeoxyuridine (FUDR) was added to the medium in a concentration of 1×10^{-5} M when noted.

could be attributed partly to an effect associated with blastogenesis, such was not the case with human tumours (Table 1: tumours 4, 12 and 15).

These results show that human cancers either contain or produce a substance which inhibits *in vitro* migration of leukocytes obtained from the individual in whom the tumour arose. Our findings with cancer are similar to results obtained after HL-A antigen sensitization¹⁷. Falk *et al.* found that inhibition of lymphocyte migration was proportional to the HL-A antigen difference between graft donor and recipient. In relating extent of malignant disease to inhibition of leukocyte migration, we found that of five breast cancer patients the one with the most advanced disease demonstrated the greatest inhibition of leukocyte migration. Although we cannot yet relate our findings to prognosis, it is possible that elaboration of a sensitizing tumour substance which prevents tumour-lymphocyte interaction may be detrimental. Such a situation may explain the paradox noted by Hellström *et al.* that lymphocytes from patients with tumours are capable of destroying autochthonous neoplastic cells *in vitro*¹⁸. Systemic release of such a substance could cause generalized reduction of lymphocyte migration and explain the decreased responsiveness of

advanced cancer patients to delayed cutaneous hypersensitivity-type antigens or to sensitization to dinitrochloro-benzene. The partial reversal by 5-fluorodeoxyuridine of inhibition of leukocyte migration may also explain the observation of Blomgren *et al.* that fluorinated pyrimidine chemotherapy enhanced the delayed cutaneous hypersensitivity response in advanced cancer patients¹⁹.

These findings raise the possibility that delayed hypersensitivity operates as a defence mechanism early in the natural history of cancer but that as the cancer becomes more advanced certain components of the reaction, specifically inhibition of leukocyte migration, become detrimental.

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Table 2 Comparison of Autologous and Homologous Leukocyte Migration

Source of leukocytes	Type of patient's tissue	
	Normal	Tumour
Patient 5	0.55 ± 0.08 (8)	0.47 ± 0.05 (7)
Control	0.38 ± 0.03 (6)	0.40 ± 0.03 (6)
Patient 11	0.25 ± 0.03 (5)	0.28 ± 0.02 (5)
Control	0.25 ± 0.00 (3)	0.28 ± 0.02 (3)
Patient 13	0.38 ± 0.04 (6)	0.28 ± 0.05 (5)
Control	0.31 ± 0.09 (2)	0.29 ± 0.06 (3)

Mean migration (cm) $\pm$ s.d. (number of replicates) of leukocytes in cell free medium in which either tumour or normal tissue had previously been incubated for 24 h. Leukocytes were obtained from either the tumour-bearing patient or from controls without tumour.

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Lentinan, a New Immuno-accelerator of Cell-mediated Responses

BCG is almost the only agent now used as the immuno-accelerator of cell-mediated responses¹⁻³, but it has various biological side effects and a complicated chemical structure,

having little influence on humoral immune responses. According to Miller¹⁴ and Waksman *et al.*¹⁵⁻¹⁷, selective depletion of thymus-derived circulating small lymphocytes and loss of cell-mediated responses have been recognized in neonatal thymectomized mice. The fact that lentinan does not cause the regression of a tumour graft in thymectomized mice and is compensated by the administration of ALS indicates that the mode of action of lentinan is part of the thymus-derived immune mechanism, in which small lymphocytes, play an important part. This is a reasonable explanation of the suggestion that regression of a tumour caused by lentinan is the result of stimulation of cell-mediated responses, so that lentinan will provide an effective reagent for cellular immunology. Further studies on the influences of lentinan in other cell-mediated responses, such as homograft rejection and delayed type hypersensitivity, are in progress. We have no

Table 1 Effect of Neonatal Thymectomy (TX) on Antitumour Activity of Lentinan

Mice	Sample	Dose	Body weight change	Average weight of tumour	Inhibition ratio	Complete regression
Normal mice	Lentinan	1 mg/kg × 10	+2.3 g	0.1 g	99.6%	9/10
	Control		+2.4 g	10.3 g		0/10
TX mice	Lentinan	1 mg/kg × 10	+1.6 g	7.3 g	6.4%	0/5
	Control		+2.8 g	7.8 g		0/5

Table 2 Effect of Antilymphocyte Serum (ALS) on Antitumour Activity of Lentinan

Sample	Dose	Body weight change	Average weight of tumour	D/A	Inhibition ratio	Complete regression
Lentinan	1 mg/kg × 10	+8.1 g	0.2 g	1/7	98.6%	5/7
ALS+	1 mg/kg × 10	+1.6 g	5.8 g	1/8	43.4%	0/8
lentinan	0.1 ml. × 10					
ALS	0.1 ml. × 10	+1.0 g	8.5 g	1/7	16.7%	0/7
NRS+	0.1 ml. × 10	+4.8 g	2.4 g	3/5	76.7%	2/6
lentinan	1 mg/kg × 10					
Control		+4.3 g	10.2 g	0/8		0/8

so that it is not necessarily the most suitable agent. We reported that lentinan^{4,5} and pachymaran⁶ strongly inhibited the growth of transplanted tumours in mice, and these two polysaccharides are worth considering as excellent immuno-accelerators.

The antitumour effect of lentinan is lost in neonatal thymectomized mice, and decreased considerably by administration of antilymphocyte serum (ALS). SWM/MS mice were thymectomized by the method of Sjödin *et al.*⁷ within 48 h of birth. After 6 weeks, 0.05 ml. (about 6×10^6 cells) of 7 day old sarcoma 180 ascites tumour was transplanted subcutaneously into the right groin of the TX mice (body weight 21–23 g), and from the following day 1 mg/kg of lentinan was injected intraperitoneally daily for 10 days. Five weeks after transplantation, the tumours were removed and their weights were compared with those of untreated control thymectomized mice to give the inhibition ratio. Table 1 shows the results and the antitumour activity of lentinan on normal mice. In normal mice, the tumour inhibition ratio of lentinan was 99.6% and regressed tumours completely in nine out of ten cases, but in TX mice the inhibition ratio was 6.4% and no tumours regressed.

Antilymphocyte serum (ALS) was prepared in Japanese white rabbits using mesenteric lymph node of SWM/MS mice as antigen⁸. As in the previous experiment, sarcoma 180 cells were transplanted subcutaneously in the SWM/MS mice and, from 24 h onwards, 1 mg/kg of lentinan and 0.1 ml. of ALS were injected intraperitoneally once a day for 10 days. Comparison of the tumour weight 5 weeks after transplantation with that of untreated control mice showed that the strong antitumour effect of lentinan was markedly reduced by ALS (Table 2).

ALS has a selective immunosuppressive effect⁹⁻¹³ and is said to suppress especially cell-mediated immune responses,

evidence that lentinan enhances the production of humoral antibody.

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Private and Public Antigens of the Mouse H-2 System

It was observed rather early in the history of the mouse histocompatibility-2 (H-2) system that some antigens of the system are limited to only one or very few H-2 alleles, whereas others are shared by several alleles¹. Antigens with limited distribution were called "private", as opposed to "general" antigens present in many different H-2 alleles². It has been tacitly assumed that the distinction between private and general antigens (the latter will be called "public" here) is an artificial one and that the difference between them would disappear when new strains and new H-2 alleles were analysed. This, however, proved not to be the case. So far H-2 alleles of some seventy strains and stocks have been determined, and the distinction into private and public antigens still holds. It can be argued, of course, that because most of the strains of the laboratory mouse are related to each other in their origin³, the differences in frequencies of individual H-2 antigens are still only apparent.

It was therefore unexpected that during the H-2 typing of wild mice, almost all of the mice reacted very strongly with most of the antisera against public antigens but only very few reacted with antisera against the private antigens⁴. It could still have been argued that because the sample of wild mice

was collected at only four different locations and because mice from the same locality showed conspicuous homogeneity in their H-2 phenotypes, the difference was again a mere reflexion of the relatedness of the mice in the sample. To clarify this point, another sample of 100 wild mice from twenty different localities in the Ann Arbor area was collected and tested.

Mice were trapped alive in Sherman traps in granaries, barns and corn cribs on farms at least 5 km beyond the city limits and usually at least 2 km apart. On a few farms, however, mice were captured at several different localities usually not more than 50 m apart. The red blood cells of the captured mice were tested with a battery of H-2 antisera of restricted reactivity (Table 1) in a direct haemagglutination test in polyvinyl-pyrrolidone (PVP)⁵. Only strong high-titred antisera were selected for this study.

The phenotypic frequencies of the twelve H-2 antigens tested for are shown in Table 2. The antigens can be clearly divided into two groups: those present in 75–95% of the localities where mice were trapped, and those present in only 0–10% of the localities. The first group—the public antigens—consists of antigens H-2.1, 3, 5, 6 and 8. These are the same antigens which are widely shared by the alleles of the laboratory mouse⁶. The second group—the private antigens—consists of antigens H-2.2, 4, 9, 17, 19, 23 and 24. The presence of these antigens in the H-2 chart of the laboratory mouse is in most cases

Table 1 Antisera Used for the Typing of Wild Mice

Code designation	Strain	Antiserum made in	H-2 allele	Strain	Immunizing tissue supplied by	H-2 allele	Antibodies present
C-1 *	(C3H.SW × B10.M)F ₁		b/f	C3H.NB		p	1,16
S-12	(B10.D2 × A)F ₁		d/a	HTH		h	2
C-3 *	(A.BY × WB)F ₁		b/w	A.SW		s	3,19
S-29	(A.BY × AKR.M)F ₁		b/m	A		a	4
S-46	(B10.D2 × HTG)F ₁		d/g	B10		b	5,33?
S-35	C3H		k/k	C3H.R3		r	6,18?
S-48	(B10 × A.SW)F ₁		b/s	A.CA		f	8,9
S-22	(B10.A × A.SW)F ₁		a/s	A.CA		f	9
S-21	(C3H.B10 × AKR.M)F ₁		b/m	C3H.Q		q	17
S-24	(B10 × A)F ₁		b/a	A.SW		s	19,7?
C-23 *	(B10 × LP.RH)F ₁		b/r	B10.BR		k	23,32
S-34	(B10.Y × C3H.B10)F ₁		p/b	I		i	24

* Antisera supplied by Transplantation Immunology Branch, National Institutes of Health, Bethesda, Maryland.

Table 2 Frequencies of Positive Reactions of Wild Mice Red Blood Cells with Antisera against Individual H-2 Antigens

Localities	H-2 antigens											
	1	2	3	4	5	6	8	9	17	19	23	24
KPA †	5/8 *	0/8	4/8	0/8	6/8	4/8	1/8	0/8	3/8	0/8	0/8	0/8
KPB	7/8	0/8	4/8	0/8	7/8	1/8	0/8	0/8	0/8	0/8	0/8	0/8
KPC	10/11	8/11	6/11	0/11	11/11	3/11	2/11	0/11	0/11	0/11	0/11	0/11
STA	5/5	0/5	4/5	0/5	5/5	5/5	2/5	0/5	0/5	4/5	0/5	0/5
STB	4/5	0/5	4/5	0/5	5/5	3/5	2/5	0/5	0/5	0/5	0/5	0/5
STC	0/4	4/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
BUA	3/3	0/3	1/3	0/3	3/3	2/3	1/3	0/3	0/3	0/3	0/3	0/3
BUB	3/3	0/3	0/3	0/3	3/3	3/3	0/3	0/3	0/3	0/3	0/3	0/3
CHA	2/2	0/2	1/2	0/2	2/2	1/2	2/2	0/2	0/2	0/2	0/2	0/2
CHB	2/3	0/3	1/3	0/3	3/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3
WOA	3/4	0/4	2/4	0/4	4/4	4/4	2/4	0/4	0/4	0/4	0/4	2/4
GAA	6/8	0/8	3/8	0/8	6/8	7/8	0/8	0/8	0/8	0/8	0/8	0/8
PTA	3/3	0/3	2/3	0/3	3/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3
DRA	3/4	0/4	4/4	0/4	3/4	4/4	2/4	0/4	0/4	0/4	0/4	0/4
WAA	2/3	0/3	0/3	0/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
WRA	1/2	0/2	1/2	0/2	2/2	2/2	2/2	0/2	0/2	0/2	0/2	0/2
DIA	1/1	0/1	0/1	0/1	1/1	0/1	1/1	0/1	0/1	1/1	0/1	0/1
KEA	5/8	0/8	3/8	0/8	5/8	6/8	6/8	0/8	0/8	0/8	0/8	0/8
SAA	7/7	0/7	3/8	0/7	7/7	5/7	4/7	0/7	0/7	0/7	0/7	0/7
SAB	2/8	0/8	5/8	0/8	2/8	2/8	3/8	0/8	0/8	0/8	0/8	0/8
Total	74/100	12/100	48/100	0/100	80/100	54/100	32/100	0/100	3/100	5/100	0/100	2/100
Positive localities (%)	95	10	80	<1	95	85	75	<1	5	10	<1	5

* Number of positive mice over total number of mice tested.

† The same first letters indicate the same farm.

Table 3 *In vivo* Absorption of Antiserum S-46 (anti-H-2.5, 33?) in Wild Mice

Absorbed in					Reaction with test cells of							
	WRA67	WAA64	DRA62	BUA17	BUA16	PTA53	CHA51	CHA2	STA34	STA39	A	B10.D2
BUA19	0	0	0	0	tr	1	3	2	1	4	2	0
CHA26	0	0	0	0	0	1	0	0	0	1	tr	0
WOA26	0	0	0	0	0	0	0	0	0	2	0	0
KPA58	0	0	0	0	0	2	2	1	1	4	0	0
PTA52	0	0	0	0	0	0	2	2	3	4	0	0
DRA63	0	0	0	0	0	0	0	0	0	tr	0	0
WAA65	0	0	0	0	0	0	3	2	2	3	0	0
WRA66	0	0	0	0	0	0	0	0	0	0	0	0
DIA68	0	tr	0	0	0	0	0	0	0	0	0	0
B10.D2	3	3	3	2	3	3	3	3	3	3	3	0
B10	0	0	0	0	0	0	0	0	0	0	0	0
B10.A	0	0	0	0	0	0	0	0	0	0	0	0

0 and tr, negative reaction; 1 and 2, weakly positive reaction; 3 and 4, strongly positive reaction in haemagglutination test.

limited to one H-2 allele and alleles derived from it by recombination⁶. Antigen H-2.23 is a new antigen defined by antiserum (B10×LP.RIII)F₁ anti-B10.BR and is limited to allele H-2^k and its recombinational derivatives¹⁰. Antigen H-2.24 is also a new antigen, defined by antiserum (B10.Y×C3H.B10)F₁ anti-I/St and limited to alleles H-2^j and H-2ⁱ (J. Klein and D. C. Shreffler, unpublished results). Three of the private antigens, H-2.4, H-2.9 and H-2.23, were absent from the tested sample. (A few weakly positive reactions with antisera against these antigens proved to be non-specific in repeated tests and/or in absorption *in vivo*.) Non-specific agglutinability of mouse red blood cells in the PVP technique is not a rare phenomenon, however; and so it could be argued that some H-2 antisera tend to react nonspecifically with erythrocytes of wild mice more often than others, thus providing the basis for what seems to be two groups of antigens, public and private.

To test this possibility absorption analyses were performed (Table 3). Antiserum S-46, which according to present knowledge should contain only two antibodies, anti-H-2.5 and anti-H-2.33, was injected intraperitoneally into wild mice (0.2 or 0.3 ml. per mouse) which were previously typed as H-2.5 positive in the direct haemagglutination test. The injected mice were bled 4–24 h later and absorbed sera were tested by the PVP haemagglutination test against other (untreated) H-2.5 positive wild mice and control inbred strains. (Although the antiserum was made against B10 tissue, usually it does not react with B10 erythrocytes, so A erythrocytes were used instead.) The wild mice in the sample can be divided into two groups according to their ability to absorb antiserum S-46: (1) those which absorb the antiserum completely, both for other H-2.5 positive wild mice and the H-2.5 positive inbred strain; and (2) those which even after absorption for 24 h leave some activity in the serum against cells from some H-2.5 positive wild mice, while at the same time clearing the serum completely for others. Absorption of antiserum S-46 in B10.A (H-2^a) mice removes activity against the cells of all the wild mice, indicating that the residual reaction after absorption in the second group of wild mice is not a consequence of anti H-2.33 in the antiserum (allele H-2^a is H-2.33 negative). Normal sera collected from the wild mice before the absorption do not agglutinate erythrocytes of any wild mice; the residual reaction in the second group must therefore be specific and cannot be caused by natural antibodies normally present in the sera of some wild mice, and also present in the sera collected after *in vivo* absorption.

Two conclusions can be drawn from the absorption experiment. First, the reaction of most, if not all, the wild mice with antiserum S-46 in the direct haemagglutination test is specific, for all the mice typed as S-46-positive in the direct test were also able to absorb the antiserum *in vivo*. Second, there is some indication that antiserum S-46 contains more than one antibody, and that, perhaps, the antigen H-2.5 is divisible into subtypes. The second point, however, requires

more attention and will be studied further, both genetically and immunologically. Absorption experiments with other antisera were also performed; the details of these will be presented elsewhere. Basically they confirm the distribution and frequencies of the individual H-2 antigens as presented in Table 2. The conclusion seems therefore to be unavoidable that the phenomenon of public versus private H-2 antigens is real and not an artefact of limited knowledge of the H-2 polymorphism.

Several important observations pertinent to the phenomenon of private and public antigens may be made. First, the number of known private H-2 antigens is constantly growing⁷, while the number of public antigens has remained practically the same since 1954. Second, genetic factors controlling the private H-2 antigens seem to be located at the extreme ends of the H-2 region, while factors controlling the public antigens seem to be centred around the *Ss* locus^{8,12}. Third, private H-2 antigens form two series, and members of the same series are mutually exclusive⁸; no such exclusiveness has yet been observed for the public antigens. Fourth, genetic factors for at least some of the public antigens appear to be located on both sides of the *Ss* locus; this observation is interpreted as evidence for duplications within the H-2 region^{9,12}. No evidence for duplications of factors for private antigens has so far been presented. Fifth, extensive serological analysis of some public antigens (H-2.1 and H-2.3) provided evidence that they are divisible into several subtypes or "families" of antigens^{10,11}; no subtypes have yet been described for any private antigens.

The difference between public and private antigens can be explained on the basis of Shreffler's duplication model of the H-2 region¹², with the following minor modifications: it is postulated that there are only two genes for private antigens, one at each end of the region, and that these genes are relatively unrelated to each other and to the rest of the region. There is virtually no cross-reactivity between the products of these genes and the products of the rest of the region. The public antigens, on the other hand, are controlled by a series of genes which arose by duplications around the *Ss* locus. There are only slight antigenic differences between the products of individual genes in this series, and there is therefore extensive cross-reactivity between them. In the natural population, one detects not only the antigen against which a given antiserum was originally made but also its subtypes. This leads to much higher frequencies of positive reactions than with antisera against private antigens.

It has been pointed out that there is a close homology between the mouse H-2 and the human HL-A systems⁸. It should be stressed, however, that this homology does not include the public antigens of the H-2 system, for there is no clear evidence for the existence of similar antigens in the HL-A system. But it is possible—as has happened so often before—that the example set by the H-2 studies will soon be

followed by similar observations in the HL-A system. It is very likely that antisera against public antigens of the HL-A system—if such antigens in this system exist—are discarded as too complex and therefore unsuitable for serological analysis.

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Does Virus Infection have Evolutionary Significance?

ANDERSON'S theory¹ that "evolution depends largely" on the transfer of genetic material by viral transduction may be plausible for microbes, but in cellular organisms there are some serious objections.

First, the argument that susceptibility to viral infection must have a selective advantage because organisms do not have the complete resistance which they could evolve is equally valid for susceptibility to bacterial infections, parasites and even predators. That an organism has not reached an imagined "perfection" is insufficient reason to impute a function to the existing "imperfection".

Second, it is improbable that the "interchange of genes 'on approval'" would promote parallel evolution in cellular organisms to any significant degree, because of the integration of genotypes (coadaptation)². It is unlikely that an alien gene or block of genes will perform well in a genetic environment with which it has never had any previous interaction.

The author's parliamentary analogy falls on the same point. Populations harbour vast amounts of genetic variation³⁻⁵. Thus to be closer to reality, the analogy should be to a parliament with a vast library of variant versions of laws, nearly all of which are being tried out constantly, in a country where many statutes interlock. An entirely new statute would have little chance of being compatible with the pre-existing complex system and would almost certainly cause chaos if it were introduced even in a somewhat altered form. The question is whether there is any "need" for entirely new statutes while the vast library of variants exists.

In this connexion, Anderson supposes that "plants and animals which are free from virus infection would evolve very slowly if at all". I suggest that the important kind of variation for evolutionary change is that exemplified by isozymes^{3,4}, as well as by concealed recessives detected in *Drosophila*⁵, and that this sort of variation is abundant in nature. The very recently published evidence of a similarly large variation in

*Limulus*⁶, an animal long thought to have had an extraordinarily stable evolutionary history, further argues against any simple relationship between the amount of genetic variation and the speed of evolution.

My last and most serious objection concerns the mechanism by which cellular organisms would evolve susceptibility to virus infection. Anderson believes that the selective advantage of infectability is in allowing novel genes to be taken in and tried out. A novel gene would have to increase the reproductive success of the host and also have to be incorporated into the host's germ cell line if genes for susceptibility are to increase in frequency in the host population. If the expression of the novel gene did not increase the fitness of the individual into which it was transferred but only that of some descendant, then there would be no selection at the level of the individual and no increase in genes for susceptibility. The only mechanism left would be group selection, a tenuous hypothesis of doubtful validity⁷.

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Hangover Effect of Hypnotics in Man

DRUGS used to induce sleep—the hypnotics—are among the most widely used of all medicaments. It has been estimated that "At a very rough reckoning about one night's sleep in every ten in Britain is hypnotic-induced"¹. This assertion stems from the number of prescriptions each year for barbiturate (20 million) and non-barbiturate hypnotics (5 million)^{1,2} and emphasizes the importance of studying the detailed clinical pharmacology of such drugs. But so far there has been little attention to the residual or hangover effect detectable the next morning. Significant impairment of performance on a battery of psychological tests was found up to 15 h after a hypnotic dose (200 mg) of chlorpromazine or quinalbarbitone given at night³. Similarly, behavioural impairment and electroencephalographic changes have been reported 12 h or more after nitrazepam or amylobarbitone sodium⁴. In these studies, however, subjects were forbidden caffeine-containing drinks for the period of the study and were thus undergoing some degree of caffeine withdrawal.

We have investigated the hangover effects of two hypnotics each given in two doses compared with a placebo: butobarbitone sodium (100 and 200 mg) and nitrazepam (5 and 10 mg), a new non-barbiturate hypnotic, which is widely used and safe in overdoses⁵. Ten normal subjects each received all five treatments (placebo, and two drugs in two doses) at weekly intervals as part of a fully balanced design, using double blind procedures. They were told not to drink alcohol on the evenings when they took the sleeping tablets but were allowed their normal intake of caffeine-containing beverages both night and morning. The drug was taken at 23.00 h and the physiological and psychological tests included the electroencephalogram both at rest and during an auditory reaction time task, and palmar sweat gland activity. Psychological tests included key-tapping rate (a measure of simple motor speed), the digit symbol substitution test (a measure of coding and associative skills) and linear scales (100 mm) on which the subjects rated themselves for quality

of sleep the previous night and feeling of alertness at the time of testing.

Many tests were affected significantly by the drugs. For example, tapping was slowed from a mean of 377 taps per min after the placebo to 344 per min after 200 mg of butobarbitone sodium ($P < 0.001$, Fig. 1). Auditory reaction time was prolonged from a mean of 219 ms after the placebo to 247 after 200 mg of butobarbitone ($P < 0.001$). Fewer items of the digit symbol substitution test were completed, for example the mean was 76 in 90 s after the placebo and 70 after 10 mg of nitrazepam ($P < 0.001$). These effects were chiefly a consequence of motor impairment, for performance times were proportionately increased much more than were errors. Subjectively, quality of sleep was generally improved by the drugs but alertness at the time of testing was diminished after only the larger doses (Fig. 2).

The electroencephalogram was analysed by dividing it into four broad wave bands using analogue filters. Significant drug-induced changes were found in the energy levels of each wave band. In general, energy in the slow wave bands (2.4–4.0 Hz; 4.0–7.5 Hz) was decreased and that in the faster bands (7.5–13.5 Hz; 13.5–26.0 Hz) increased. For example, the proportion of fast wave activity (13.5–26.0 Hz) was increased by both drugs and this variable proved very sensitive to drug effects (Fig. 3).

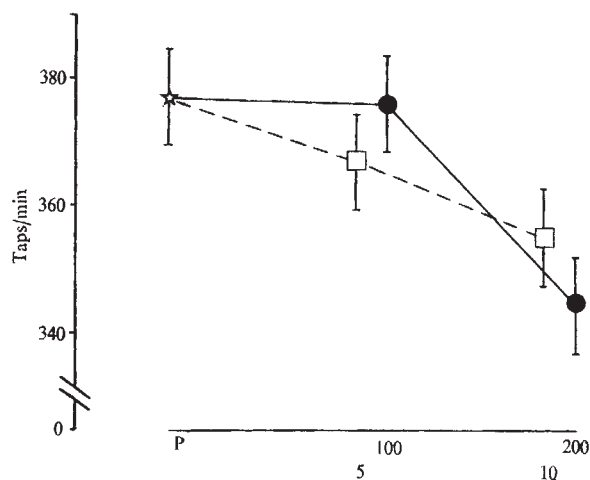


Fig. 1 Effects of hypnotics the following morning on tapping rate. The means and standard errors for ten normal subjects are shown for placebo (★), butobarbitone sodium (●, 100 and 200 mg), and nitrazepam (□, 5 and 10 mg).

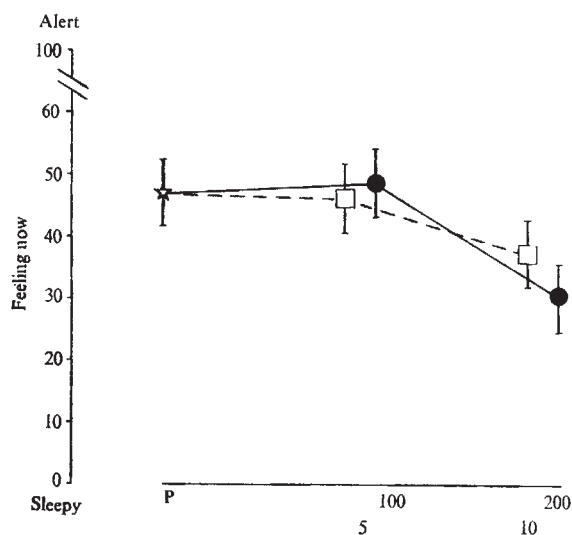


Fig. 2 Effects of hypnotics the following morning on rating of subjective feelings of alertness. The ordinate scale is in terms of mm from the "sleepy" end of the linear scale. Symbols as in Fig. 1.

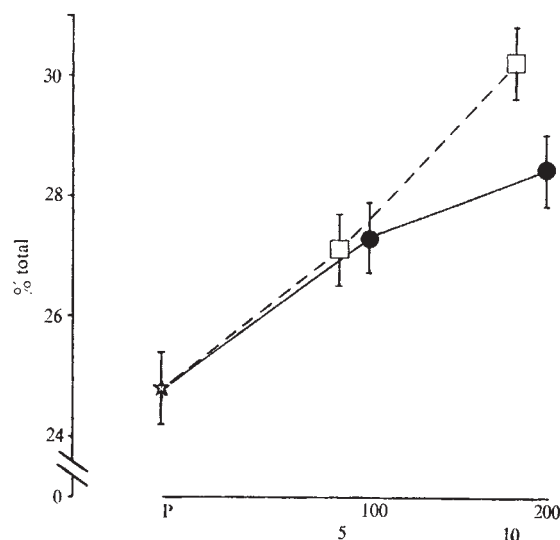


Fig. 3 Effects of hypnotics the following morning on the 13.5–26.0 Hz wave band of the electroencephalogram. The mean rectified voltage in this wave band is expressed as a percentage of that of the entire electroencephalogram. Symbols as in Fig. 1.

Thus definite hangover effects are demonstrable 12 h after hypnotic doses of a barbiturate and a new, widely used, non-barbiturate hypnotic. These effects are consistent with the pharmacokinetics of these drugs: nitrazepam, for example, has a half life of 6–10 h⁶.

The doses used were in the recommended clinical range. Our study with a small number of normal subjects gave some indication of the magnitude of effects to be expected. Caffeine was not withdrawn because such deprivation changes drug status. Our results indicate that a normal intake of caffeine does not counteract the appreciable hangover effects of hypnotics; it is not known what an increased amount of caffeine would do. It is difficult to extrapolate from normal subjects to patients suffering from persistent insomnia, as sleep deprivation itself may impair performance the next morning. Nevertheless test performance after the worst night's sleep (self rating) was superior to that following satisfactory sleep with a hypnotic. It is hoped eventually to investigate the chronic use of hypnotics in insomniac patients in whom the processes of cumulation and tolerance might have counteracting effects. Meanwhile we must remain aware that, although these hypnotics lessen the distress of the insomniac patient, psychological impairment and electrophysiological changes are inevitably left the next morning. Indeed, it is unrealistic to expect any adequate hypnotic drug to be devoid of pharmacological effects on wakening.

This study was carried out while A. J. W. held a Roche research fellowship; the work was supported by Roche Products Ltd which supplied the drugs, and by the Medical Research Council of which M. H. L. is a member of the external scientific staff.

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BOOK REVIEWS

Lancashire Hot-pot

University Perspectives. By John Knapp, Michael Swanton and F. R. Jevons. Pp. x+297. (Manchester University: Manchester; Barnes and Noble: New York, November 1970.) £3.00.

FOR roughly the last quarter of the nineteenth century, the precursors of the universities of Leeds, Liverpool and Manchester were combined as constituent parts of the Victoria University. It must have been a very loose federation because each college was sustained by fierce local pride, and, in retrospect, dissolution of the alliance seems inevitable. It took place as soon as it decently could after the demise of the Good Queen and Manchester was left with its own university. It is unique amongst English universities outside Oxford, Cambridge and London in consisting of two parts still affectionately called "Owens" and "Tech" by many former students. The latter is now the University of Manchester Institute of Science and Technology (UMIST) and for sixty-five years it has been the Faculty of Technology of the University of Manchester, though it has been called successively the Municipal School of Technology and the Manchester College of Science and Technology; names which emphasized its difference from the University of Manchester. Even now, many departments in UMIST are duplicated in Owens and to the outsider they seem often to operate as two independent institutions.

Mancunians will also claim that the University of Manchester has always held primacy of place amongst the great civic universities, and even a Yorkshire reviewer will concede this to be true for almost all the first half of this century. Many factors contributed to this. The city of Manchester was the centre of a great conurbation which, through its trade, looked outwards, and which possessed vigorous industries frequently founded by European immigrants who brought with them a love of music, literature and art and, encouraged by the *Manchester Guardian*, the city developed a real belief in itself as the country's pacemaker in the sciences

and humanities, and in its university as one of its chief instruments of progress. Those who doubt this should read Mary Stocks's *My Commonplace Book*, where the impressions made on a Londoner by Manchester and its university are made abundantly clear. Immigrant scholars, scientists and engineers were made welcome and much esteemed in the university and, aided by its Literary and Philosophical Society with its glorious links with Dalton and Joule, the university encouraged the interested citizenry of Manchester to know what its savants were about and to share in their successes. Its science departments were especially distinguished; it was naturally expected in Manchester that professors in physics and organic chemistry, if not Nobel laureates already, would, in due course, be so honoured. Perhaps the most important factor in the success of the university was that the academic staff numbers were not incomprehensibly large; Alexander the philosopher could and did talk with Rutherford the physicist.

With UMIST, Manchester University is now the largest of the civic universities, and indeed exceeds both Oxford and Cambridge in size. But, as one who loves, admires and occasionally despairs of civic universities, I have not perceived that it has maintained its former pre-eminence. Partly this is due to the fact that the other universities have begun to catch up, partly that "formula financing" which has necessarily underlain much of UGC thinking in the last decade is a powerful force towards uniformity of university levels, but partly, as the editors of this book clearly feel, because the social unit comprehensible to a staff member in Manchester is now the department, and that outside the narrow professional context, communication, both intra- and extramurally, is often non-existent or ineffective. This book consists of twenty essays by Manchester academics aimed at reducing this unprofitable isolation. Inevitably it is a pot-pourri lacking the consistency of quality of ingredients of a good hot-pot. But unevenness is interesting and the variety of styles gives unparalleled insights into Liam Hudson's convergent and divergent

minds. It is invidious to select but I must report that I found the essays on government and history extremely interesting—that on history takes the form of a conversation about the Manchester history school involving Tom Jones, Thwackum and Square—whereas that on economics is arid and dull and does little justice to the distinguished work carried out in this field in Manchester. The last essay is by a theologian and in many ways is also the best because it is almost the only one, apart from Professor Cox's on English, which recognizes that many young people now at universities are seeking meaning and purpose in their lives. Sad to relate, many go away with minds full of tribology and marginal costs or orbital symmetries or whatever, but with little awareness of their own identity. Perhaps the theological essay serves to remind us all that possibly university teachers only have an incentive to think about their subjects in a wider context when their subjects become sufficiently unpopular! Meanwhile, horizons of Owens and Tech academics could be broadened by reading *University Perspectives*, and I suspect that this would also apply to many readers of *Nature*.

F. S. DAINTON

Contemporary Marxism

Marx and Contemporary Scientific Thought. (Publications of the International Social Science Council, No. 13.) Pp. xi+612. (Mouton: The Hague and Paris, 1969.) 89 francs.

THREE years ago this May in Paris, while students battled with police in the streets, a distinguished group of forty-five scholars from twenty-one nations took part in a symposium on "The Role of Karl Marx in the Development of Contemporary Scientific Thought". I suspect that, for many years to come, historians will be smiling over this coincidental unity of theory and practice.

In the meantime, it is good to have at last the collected proceedings of this conference. I should perhaps offer two preliminary warnings about the book. The first is that about half of the essays have been written in or translated into French. Because some of the trans-

lated material was originally composed in rather complex German, it is clear that a fair reading knowledge of the French language will be required. Second, *Marx and Contemporary Scientific Thought* scarcely touches upon theoretical and/or experimental developments in the natural sciences. "Scientific thought" in this instance relates almost exclusively to the social sciences.

Despite those two provisos, I hope that this bulky volume will attract a certain portion of *Nature's* audience. For the work crystallizes out a set of theoretical tendencies potentially as important to social scientists as the May Days were to young revolutionaries. I refer here to the first major re-evaluation of Marxist social theory since the 1930s. Interestingly enough, the leading theorists behind this re-orientation were themselves students and young lecturers shortly before the Second World War. Since that time, Marx's writings have served them not as an orthodoxy but as an essential point of departure. Thus three leaders of the new movement—Adorno, Habermas and Marcuse—while subscribing to Marxism in general terms, have felt free to alter Marx's concepts of, for example, revolution and the labour theory of value.

The outline of the neo-Marxist synthesis is only now emerging, perhaps because many of its practitioners, such as Eric Hobsbawm, are historians who have regularly eschewed the role of theoretical sociologist. In his essay for the work under review, Hobsbawm does attempt to explain the ideological presuppositions behind his own work. The end result, however, is less the synthesis of a new view than the destruction of several prevailing ones. As an example of theory building of considerable power, Jürgen Habermas's piece on "Technique et Science comme 'Ideologie'" should be consulted.

Whatever may be said about the direction of the "new Marxism", it is evident that it stands little chance of becoming the new Communist orthodoxy within the foreseeable future. To judge from the papers presented by the Russians at the Paris conference, the wave of the present in Eastern Europe is iconography, not iconoclasm.

PAUL GARY WERSKEY

Fine Fare

Synthetic Food. By Magnus Pyke. Pp. viii + 145. (John Murray: London, December 1970.) £2.25.

WE know, or think we know, all the essential components of an adequate diet and so can discuss the feasibility and wisdom of making synthetic food.

Every component except B₁₂ can now be manufactured; no doubt even that strange molecule will be synthesized soon. Two questions now arise: first, which nutrients are more economical to synthesize rather than to grow? And second, would the synthetic product be available to people in all parts of the world where it is needed? Pyke uses "synthesis", with commendable strictness, to mean production by purely chemical processes (though the parent substance may be a product of agriculture such as glucose); he does not therefore include conversions brought about by fermentation. In principle, the starting products could have been CO₂, NH₃ and so on. In essence, Pyke agrees with the remark attributed to Steinmetz, in conversation with Baeyer: "You can make indigo more cheaply than God, you will probably be able to make rubber more cheaply than God, but you won't make starch or cellulose more cheaply than God". Few other limitations on synthesis are foreseen.

Cheapness depends on the scale of production and the amount of effort put into improving the processes used. The effort expended depends partly on the natural impulse of an expert to be as efficient as possible; it is also stimulated by competition. A scientifically based industry is likely to be so superior to peasant farming and processing techniques that the peasant industry disappears. There is then little incentive to start the agronomic and biochemical work that would be needed to give the "natural" product any hope of being competitive. But it is legitimate to wonder whether, in every instance where synthesis has prevailed, the "natural" product would not have been cheaper had a comparable amount of research been done on it—especially research aimed at producing multipurpose plants.

When food is being handled by mass production methods and is being distributed through supermarkets, synthesis is probably the cheapest way of obtaining many of the factors that can advantageously be added to it; there is no reasonable alternative to synthetic vitamin A or C in packaged foods. Similarly, the nutritional value of many of the protein sources destined for inclusion in "broiler" rations is greatly enhanced by adding small amounts of methionine. Pyke is so carried away by these facts that he tends to overlook the fact that the people most in need of help do not eat packaged foods and could not use "broiler" methods of animal feeding. The first paragraph of his book asserts that the "complex life of a modern community" would be just as impossible without adequate housing, paper, clothing and transport as without adequate food. That may be true;

but it is possible to be less complex. He glosses over the fact that peoples' food requirements are similar wherever and however they live; the amount of clothing and paper that they use varies dramatically. This parochial outlook leads him to disparage various projects for local production of better foods from local products by simple means. Overlooking his own usefully reiterated figures showing the steady diminution in the costs of making amino-acids and vitamins, he says these novel foods are too expensive. How can one tell until they have been made in bulk? The important point is that local methods do not depend on the continuing goodwill of outsiders.

To round off this survey of the place of synthetics in supermarket nutrition, there is a chapter on "non foods"—edible rubbish guaranteed to do the consumer no good. The long term consequences of a community with its guts stuffed with alginates, methylcellulose and plastics are not discussed—but bacteria have interesting adaptive abilities!

N. W. PIRIE

The Arctic at Risk

Productivity and Conservation in Northern Circumpolar Lands. By W. A. Fuller and P. G. Kevan. (Proceedings of a Conference held at Edmonton, Alberta, 15–17 October 1969. IUCN Publications, New Series No. 16.) Pp. 344. (International Union for Conservation of Nature and National Resources: Morges, Switzerland, 1970.)

THIS symposium of thirty-six short papers covers a very wide range of subjects, chiefly concerned with ecological problems of conservation in terrestrial regions of the arctic and subarctic, and to a lesser extent with measurements of the primary and secondary productivity of the principal ecosystems. It brings together reports from work going on in Alaska, the Canadian arctic, Greenland, and the arctic parts of Europe and Siberia.

The first contributions include a brief but masterly review of the essential features of the climate of the tundra zone, illustrated by a series of maps, and a review of the complex interrelations between permafrost and vegetation. This is followed by several papers devoted to the general characteristics of vegetation with a special emphasis on primary productivity and the limitation imposed by the very short growing season, low irradiance and low rates of nutrient turnover. Research on mammals is summarized in papers on reindeer, lynx, polar bear and arctic fox. Finally, the problems of conservation are reviewed in terms of wild life management, utilization of mineral resources and human population.

The symposium as a whole carries a clearly defined and urgent warning which is well supported by the evidence presented. Vegetation and animal populations in arctic lands are beautifully adapted as a delicately balanced whole to a very harsh environment. Exploitation of the animal populations by hunting, though sometimes regrettable in its insensitivity to their decline, has not caused losses that could not be reversed through international cooperation. But the exploitation of the mineral resources of the arctic and development of land communications causes damage of a different order of magnitude. Heavy vehicles, by destroying vegetation and compacting the humus, so alter the thermal conductivity of the ground that the heat balance is changed and melting of the permafrost is initiated. A single passage of a vehicle can start a process of irreversible thermal erosion, leading in a few years to the formation of gullies many feet in depth. The disposal of waste presents a special problem when all decomposition is prevented by low temperatures, and there are no bushes to cover up the heaps of discarded oil drums and other refuse. Bad habits which may pass in the temperate regions become intolerable in the arctic.

It seems proved beyond reasonable doubt that the land surfaces of the arctic are extremely vulnerable to many normal activities of modern man. The vegetation and animal life are at the limit of their tolerance and their survival depends on their precise adjustment to small scale features of the environment. A very slight change in this environment usually has quite disproportionate effects and may result in devastation. The exploitation of the arctic regions requires a thorough scientific analysis of these problems, if irreversible damage is not to become widespread.

C. D. PIGOTT

Wright Preserved

An Original Theory or New Hypothesis of the Universe, 1750. By Thomas Wright. A Facsimile Reprint together with the first publication of "A Theory of the Universe, 1734". Introduction and Transcription by Michael A. Hoskin. (History of Science Library: Primary Sources.) Pp. xxxvii+178+31 plates. (Macdonald: London; Elsevier: New York, February 1971.) £10.00.

THIS addition to the Elsevier History of Science Library is primarily a facsimile of Thomas Wright's *An Original Theory of the Universe*, which was published in 1750 and which made Wright famous as the first person to appreciate the true nature of the Milky Way; an effect resulting from the

immersion of the solar system in a much greater star system. Generally, Wright is perhaps credited with rather more than his due measure of respect in this context, for he did not conceive the idea of our galaxy as a disk of stars, but rather preferred to explain the observations in terms of a "galaxy" made up of spherical shells of stars. This does not, however, detract from the historical importance of his work.

But if he has received more than his share of the credit for discovering the nature of our galaxy, Wright's more far reaching theories of the universe have tended to be overlooked, his name being firmly established on the basis of one great discovery, rather than receiving the more general acknowledgment which his widely ranging ideas merit. Notably, his speculation that "the endless Immensity is an unlimited Plenum of Creations not unlike the known Universe" comes close to the realization that the universe (in the modern sense) is populated by galaxies of which our own is an unremarkable individual example. Although the mystic and religious associations brought into his work prevented Wright from making this final theoretical step, his work is well worth the wide attention which this reproduction should bring to it.

Dr Michael Hoskin's excellent introduction adds considerably to the merit of the volume as a whole, setting the theory of Wright in its historical perspective, and providing a very complete account of how the ideas developed from their first primitive form. In this context, it is fascinating to read the first ever publication of Wright's "A Theory of the Universe", written in 1734, when the author was only 22 and had received little formal education in the subject in which his ideas became so prominent. There can be few scientific works which have waited for over two hundred years for publication; as late as 1898 this manuscript was purchased, together with the bulk of Wright's papers, by Newcastle Central Library for only £3.00. A bargain then, the belated publication of the work provides an added bonus now for purchasers of this volume.

Apart from its importance to the history of astronomy, this facsimile is a very high quality reproduction of the original, the proliferation of plates being remarkable for an eighteenth century work. As the beautiful original is now exceedingly rare, bibliophiles will certainly welcome this copy. Astronomers may be more interested in the opinion that "could we view Saturn thro' a Telescope capable of it, we should find his Rings no other than an infinite Number of lesser Planets, inferior to those we call his Satellites", while, having been shown in "Letter

the Fourth" that the Sun lies at the centre of a family of planets and comets, they may well be prepared to answer the question of the likely content of space near other stars in the way Wright proposes—"Your Answer, I think I may venture to say, would not be nothing; and methinks I already hear you say, Why Planets such as ours."

JOHN GRIBBIN

For Want of Iron

Iron Deficiency: Pathogenesis, Clinical Aspects, Therapy. By L. Hallberg, H. G. Harwerth and A. Vannotti. Pp. xi+628+16. (Academic: London and New York, December 1970.) £6.00; \$18.50.

IN 1963, a Ciba Symposium on "Iron Metabolism" was held in Aix-en-Provence, and in due course the proceedings were published (*Iron Metabolism*, Springer-Verlag, Berlin, 1964). The fifty-eight participants gave an up to date account of the basic and clinical aspects of the subject. This newer publication is an account of the papers given at a similar symposium organized by Geigy in Arosa, Switzerland, in 1969. On this occasion there were seventy-six experts taking part, twelve of whom had attended the earlier meeting. In each instance, the discussion following the papers is published, and it is of considerable interest to see the extent of progress during six years. Fortunately, each book contains an index. All the papers in *Iron Deficiency* are in English. There are three sections which deal respectively with the "Pathogenesis", "Clinical Aspects" and "Therapy of Iron Deficiency", and the following 38 pages are taken up with an account of a panel discussion on "Iron Therapy in Clinical Practice".

This is an essential book for anyone working in this field of interest, the amount of knowledge that is contained in it being very considerable. As might be expected, all aspects of iron metabolism are dealt with in detail, including iron stores, biochemical functions, regulation of iron transport, factors affecting absorption, and the supply and utilization of food iron, together with requirements during growth and pregnancy, and menstrual and other losses. The discussions are of considerable interest, highlighting, as they do, current gaps in knowledge. This more basic material occupies about 400 pages. The clinical section includes accounts of the prevalence of anaemia in certain European countries, but the chief value of the publication lies in the earlier part of the book. The size, comprehensiveness and value of the chapters vary tremendously: the largest contribution, by H. C. Heinrich of Hamburg, deals with intestinal absorption of iron in man and extends through 80 very detailed pages

of information. The smallest contribution, by Dresch of Paris, deals with the prevalence of iron deficiency in France and contains about 350 words.

One aspect of the subject, about which various workers are not in agreement, concerns the factors that affect iron absorption, and particularly the importance or otherwise of gastroferrin. This is referred to and discussed by various workers.

In summing up the views expressed at this excellent symposium, Carl Moore makes the important point that, unlike man, many experimental animals absorb ferric and ferrous iron equally well. He refers, too, to the degree of sophistication of ferrokinetic studies and how studies of iron absorption have been facilitated by the development of whole body counters. RONALD GIRDWOOD

Nematodes in Action

The Behaviour of Nematodes: Their Activity, Senses and Responses. By Neil A. Croll. Pp. ix+117. (Arnold: London, November 1970.) £2.25.

THE author has collected the scattered information about the behaviour of animal, plant and free living nematodes and presented it as a review for research workers and students. The book is mostly about movement and the responses of nematodes to external stimuli; descriptions of many behaviour patterns such as feeding are omitted. Nematode responses are discussed in individual sections each devoted to a stimulus type, light, temperature, chemical, electric, gravitational and mechanical. Other sections describe movement activity, aggregation and orientation. Most relevant papers seem to be included in the bibliography, and the book is a useful source of references for further study. There are indices to both subjects and species.

The style is pleasant and the text readable although occasionally verbose and vague, or so brief that an idea is not fully defined and statements appear contradictory. A few words are misused and some jargon introduced but less than in many scientific publications. Often Croll has been shy about using his experience to guide readers so that after reading his summary of published work we have to draw our own conclusions and decide where further research is needed. He has, however, introduced new ideas into some sections deriving information from work on animals other than nematodes.

The index is adequate but has several pagination errors and omissions. Some indication of the pages where a subject is discussed in detail would help the reader, but printing and proof reading errors are few. C. D. GREEN

Molecular Spectroscopy

Physical Chemistry: An Advanced Treatise. Vol. 4: Molecular Properties. Edited by Henry Eyring, Douglas Henderson and Wilhelm Jost. Pp. xix+832. (Academic: New York and London, September 1970.) £18.20.

THIS volume contains fourteen chapters written by a number of authors. There is an introduction by S. H. Bauer to the various topics covered, which include molecular rotation by C. C. Costain, vibrations of molecules by G. W. King and vibrational spectra by J. R. Hall. Radical spectra are covered by D. E. Milligan and H. E. Jacox, and T. Shimanouchi writes on molecular force fields. The interactions between electronic, vibrational and rotational motions, and the electric moments of molecules are considered by J. T. Hougen and A. D. Buckingham respectively. There are accounts of nuclear magnetic resonance (R. M. Golding), electron spin resonance (H. G. Hecht), nuclear quadrupole resonance (E. Schempp and P. J. Bray), Mössbauer spectroscopy (N. N. Greenwood), molecular beam spectroscopy (C. R. Mueller) and, finally, electron diffraction in gases (S. H. Bauer).

The volume is well edited, the nomenclature and symbolism being consistent throughout, but it is disappointing that SI units and equations appear only (as alternatives to c.g.s. units) in Buckingham's chapter. What is difficult in books of this type is to establish amongst the authors a common view of the level and standard of the articles required. Here the editors have been less successful: articles range from excellent introductions, written with authority, to reviews, some thorough, some not and some which assume so much prior knowledge as to make them useful to research workers in the field only.

Although the articles do not attempt to be encyclopaedic, they should summarize the state of development of each topic. The n.m.r. chapter, which makes the subject seem unduly complex, fails to deal with solid state studies and considers but perfunctorily studies of partially orientated molecules (it also gives the symbol "J" a novel meaning). The e.s.r. chapter takes no account either of gaseous species or of neutral radicals in solution; optical methods only are discussed in the study of the spectra of radicals: and no experimental evidence is given for the breakdown of the Born-Oppenheimer approximation, although the theory of the effects is discussed with insight. The chapter on molecular beam spectroscopy lacks detail. I recommend the chapters by Costain, Buckingham, Shimanouchi, Schempp and Bray and Greenwood; the chapter by King

includes a very clear introduction to Group Theory.

At a third of the price, this volume could be on every undergraduate's bookshelf, alongside a good book on magnetic resonance. As it is, all readers should leave its purchase to the richer libraries. K. A. McLAUCHLAN

Geochemical Data

Handbook of Geochemistry. Volume II/2. Executive editor: K. H. Wedepohl. Editorial board: C. W. Correns, D. M. Shaw, K. K. Turekian and J. Zemann. Pp. iv+667. (Springer-Verlag: Berlin and New York, 1970.) Loose-leaf binder, 212 DM; \$58.30.

MY chief criticism of the first loose-leaf instalment of volume two of the *Handbook of Geochemistry* was that all material for an element had not been collected before publication of that particular chapter. The appearance of part two hardly eases the frustration engendered by this continuing procedure. Only three further chapters (iron, tin and mercury) have been completed to be added to the finished contributions on carbon, scandium, germanium and rhenium. Partial data for twelve new chapters are now published, but there are still twenty-five elements (including nitrogen, silicon, nickel and copper) for which there is yet no information.

On the production side Springer-Verlag will not win friends with this second instalment. First, the price of the new part (slightly under nine cents per page, as against less than five and a half cents for volumes one and two, part one) has risen at a rate that seems excessive, even in these days of cost inflation. Are subsequent instalments to suffer similar price increases of almost sixty per cent over twelve month periods? Second, surely the publishers could have ensured the same positioning for the punch holes of the pages in the two published parts. So poor is the positioning in the separate parts that when the chapters are arranged in their correct element order, there is a five millimetre variation in the registration of the page margins. Furthermore, thirty-eight sheets are punched on the wrong vertical margin so that the chapter "Yttrium and the Lanthanides" has to be read from back to front, unless it is removed from the file.

The scope of the work, its high standard of text and figure presentation, and the extensive literature coverage are still matters for editorial congratulation. Publication of part two on schedule is also commendable.

DUNCAN MURCHISON

Obituary

Dr G. A. Reay

GEORGE ADAM REAY, formerly director of the Torry Research Station, Aberdeen, died on January 20 after a brief illness. He was sixty-nine.

He was one of the small, enthusiastic and outstanding team of British workers which, initially under the leadership of the late Sir William Bate Hardy, pioneered the study of the various aspects of food science and technology. He obtained his MA (1921) and BSc (1923) at Aberdeen University and won a Senior Kilgour Scholarship. In 1924 he was awarded a Studentship of Emmanuel College, Cambridge, and studied aspects of pancreatic activity and carbohydrate metabolism under the late Sir Frederick Gowland Hopkins at the Sir William Dunn Institute. He was awarded a Carnegie Research Fellowship in 1926 and obtained his PhD (Cantab) in 1927.

In September of the same year he joined the Food Investigation Organization of the Department of Scientific and Industrial Research and was posted to Aberdeen to study the possibility of improving methods of handling "white" fish at sea. It was characteristic of the man that he began his investigations at sea on commercial trawlers rather than in the laboratory; this early work threw much needed light on some of the basic factors affecting spoilage and it led to

recommendations for good handling practice that have required little modification over the years. When Torry Research Station was opened in 1929, Reay had already gained valuable field and research experience in freezing and cold storage; he was one of the first to stress the importance of low temperature storage to obtain a good product, as well as rapid freezing, a view at variance with contemporary thinking, and he led the work on freezing at sea, which was first applied commercially in the early 1960s.

Dr Reay is survived by his wife, son and daughter.

Academician A. I. Alikhanov

THE death occurred, on December 8, 1970, of Academician Abram Isaakovich Alikhanov, one of the leading physicists of the Soviet Union.

Alikhanov was born in 1904, in Gandzha (now Kirovabad), in Azerbaijan. He was educated at the Leningrad Polytechnic Institute. After his graduation in 1931, he specialized in nuclear physics and cosmic radiation. In 1934–37 he was the first to study the basic laws of positron formation by means of gamma rays, and investigated problems of beta-decay. With his brother, Artemii Isaakovich Alikhanyan, he began a programme of systematic study of the

beta-spectra of synthetic radioactive elements. During World War II, he set up a laboratory in Armenia where he developed a new method of studying the composition and energy spectra of cosmic rays.

In 1945, Alikhanov founded the Institute of Theoretical and Experimental Physics, remaining as its director until 1968. There, he and his brother developed a large spectrometer for studying the mass spectra of cosmic ray particles. In 1949 he put into operation the first Soviet reactor with a heavy water inhibitor, and was one of the designers of the first Soviet atomic bomb. In 1961, on his initiative, the Institute of Theoretical and Experimental Physics produced a 7 GeV proton synchrotron, and he later took a leading part in the development of the Serpukhov 70 GeV proton accelerator.

He was elected to the Academy of Sciences of the Soviet Union and the Armenian Academy of Sciences in 1943, and became Chairman of the Commission for the Study of Cosmic Rays of the Academy of Sciences of the USSR in 1959. His publications include *Investigation of Artificial Radioactivity* (1936), *New Data on the Nature of Cosmic Radiation* (1945), *Cosmic Radiation* (1949), *Weak Interactions* (1960) and *Experiment* (1962). He was awarded the Order of Lenin three times, a State Prize for physics and a number of medals.

Announcements

University News

The Council of the University of Birmingham has approved the appointment of a review body "to consider the role, constitution and functioning of the University of Birmingham and to make recommendations to Council for any desirable changes". The review body would now welcome written submissions of evidence from any person or organization concerning any part of the matter within its terms of reference. Written evidence should be sent to the secretary, Sir Maurice Dean, Winterbourne, 58 Edgbaston Park Road, Birmingham B15 2RT, not later than March 31. Persons or representatives of organizations may later be invited to appear before the review body.

Appointments

Professor Henry Charnock, University of Southampton, has been appointed director of the National Institute of Oceanography in succession to Sir George Deacon.

Miscellaneous

The Zoological Society of London has made the following awards for 1970: *the Stamford Raffles award*, to Mr D. R. Rosevear, an amateur zoologist, for his contributions to the knowledge of West African mammalian fauna; *the scientific medal*, to Dr Denis Noble, University of Oxford, for his work on the physiology of nerve and muscle and to Professor J. G. Phillips, University of Hull, for his work on comparative zoology; *the Thomas Henry Huxley award*, to Dr P. J. Sharp, University of Leeds, for his doctoral thesis "The hypothalamic control of gonadotrophin release in the Japanese quail (*Coturnix coturnix japonica*)"; a certificate will be presented to Dr O. Anne E. Rosa, University of London, whose doctoral thesis was highly commended; *the Prince Philip prize*, to Stephen M. Cliff, Archbishop Holgate's Grammar School, York, for his essay "Some characteristics of the shells of limpets, *Patella vulgata*, in relation to the environment".

ERRATUM. In the article "Menstrual Synchrony and Suppression" by Martha K. McClintock (*Nature*, 229, 244; 1971),

the last sentence of the fourth paragraph should read: "In addition, subjects estimated how many times each week they spent time with males (for example, dating, visiting informally or conversing at length with male professors) and listed by room number the girls ($N \leq 10$) with whom they spent the most time, indicating which two of these they saw most often".

International Meetings

April 5–6, **Flames, Flammability and Fires**, Swansea (Professor D. F. Cullis, Department of Chemistry, The City University, London EC1).

April 6, **New Materials and Trends in the Water Industry**, London (Mr E. S. Hall, 69 Disraeli Crescent, High Wycombe, Buckinghamshire).

April 14–16, **Tissue Growth and Interaction during Development and Interactive Behaviour of Cells**, Aberystwyth (Professor Bryn Jones, Department of Zoology, University College of Wales, Aberystwyth, Wales).

May 12, **Environmental Health**, Detroit (Alan J. Hitsky, Information Services, Wayne State University, Detroit, Michigan 48202, USA).

British Diary

Monday, March 1

How to Enjoy Food Additives (6.30 p.m.) Professor B. C. L. Weedon, Society of Chemical Industry, London Section, jointly with the Food Group, at 14 Belgrave Square, London SW1.

Telecommunications—New Practices, Old Concepts (5.30 p.m.) Professor J. Greig, Institution of Electrical Engineers, at Savoy Place, London WC2.

The Use of Computers in Aircraft (7 p.m.) Mr B. J. Calvert, Institution of Electrical Engineers, at the Royal Star Hotel, Maidstone, Kent.

Tuesday, March 2

Adaptation in Mammals (5.30 p.m.) Professor R. J. Harrison, Royal Institution, at 21 Albemarle Street, London W1. (Lecture for Sixth Form Pupils from Schools in London and the Home Counties. To be repeated on March 3, 9 and 10.)

Environment in Ships (6.30 p.m.) Society of Environmental Engineers, at BAC, Bristol.

Excavations at Swanscombe 1970 (5.45 p.m.) Dr J. d'A. Waechter, University of London, at the Institute of Archaeology, 31–34 Gordon Square, London WC1.

Industrial Innovation (5.30 p.m.) Professor C. Freeman, Institution of Electrical Engineers, at Savoy Place, London WC2.

Technical Codes of Practice in Independent Television (5.30 p.m. discussion) Institution of Electrical Engineers, at Savoy Place, London WC2.

Wednesday, March 3

A British Railway's Development—The Advanced Passenger Train (7.30 p.m.) Dr S. Jones, Institution of Electrical Engineers, at Dorking Halls, Dorking, Surrey.

Colour in Architecture, Mr D. L. Medd; **Studies on Surface Texture by Goniospectrophotometry**, Mr M. P. Wassall (3 p.m.) Colour Group (Great Britain),

in the Physics Department, Imperial College, Prince Consort Road, London SW7.

Giovanni Battista Morgagni's "De Sedibus et Causis Morborum per Anatomen Indagatis", Venice, 1761 (1 p.m.) Professor J. Steudel, Royal Institution, History of Science Discussion Group, at 21 Albemarle Street, London W1.

Loran C—Some Recent Developments and Field Observations (6 p.m.) Mr W. F. Blanchard and Mr A. R. Woods, Institution of Electronic and Radio Engineers, at 9 Bedford Square, London WC1.

Medical and Veterinary Applications of Clean Air (2.30 p.m. symposium) Society of Environmental Engineers, in the Mechanical Engineering Department, Imperial College, London SW7.

Recent Advances in Microscopical Techniques of Particle Characterization (2.30 p.m.) Society for Analytical Chemistry, Particle Size Analysis Group, in the Link Lecture Theatre, The University, Leicester.

Solid State Control of Electrical Appliances (5.30 p.m. discussion) Institution of Electrical Engineers, at Savoy Place, London WC2.

Thursday, March 4

Art and Science Now: the Possibility of Convergence (1.30 p.m.) Mr P. D. Carpenter, University of London, at Imperial College, London SW7.

Have Physicists Lost Their Imagination? (1.20 p.m.) Professor D. H. White, University of London, in the Botany Theatre, University College London, Gower Street, London WC1.

Mechanical Behaviour of Polymers under Low Temperature High Frequency Cycling (6.30 p.m.) Mr J. L. Prosser, Oil and Colour Chemists' Association, at the Royal Turks Head Hotel, Grey Street, Newcastle upon Tyne.

Recent Developments in Ergot Research (5.30 p.m.) Dr Albert Hofmann, University of London, at the School of Pharmacy, 29–39 Brunswick Square, London WC1.

Reflection, Refraction and Polarization of Light. Refraction and Scattering of Light (1 p.m. films) Royal Institution, at 21 Albemarle Street, London W1.

Solvent-free Coatings (7 p.m.) Dr F. Blomryer, Oil and Colour Chemists' Association, at the British Rail School of Transport, London Road, Derby.

The Post Office as a Business (5.30 p.m.) Mr A. W. C. Ryland, Institution of Electrical Engineers, at Savoy Place, London WC2.

The Response of Scientific Advances in the Field of Water Management (6 p.m.) Sir Norman Rowntree, British Hydromechanics Research Association, at the Royal Institution, 21 Albemarle Street, London W1 (Third Fluid Science Lecture).

Friday, March 5

New Frontiers for Research and Development (9 p.m.) Dr H. E. Thiemann, Royal Institution, at 21 Albemarle Street, London W1.

Psychoactive Substances from the Plant Kingdom (5.30 p.m.) Dr Albert Hofmann, University of London, at the School of Pharmacy, 29–39 Brunswick Square, London WC1.

Reactions of Radicals Derived from Carcinogenic Aromatic Amines (1 p.m.) Mr M. J. Carey, Royal Institution, Photochemistry Discussion Group, at 21 Albemarle Street, London W1.

Monday, March 8

Communication of Objectives—Reconciling the Interests of the Organization and the Engineer (5.30 p.m.) Dr D. Pym, Institution of Electrical Engineers, at Savoy Place, London WC2.

"Ford Commuter" — Electric Urban Vehicle (6.30 p.m.) Mr T. K. L. Dobedoe and Mr R. F. Robbins, Institution of Electrical Engineers, London Graduate and Student Section, at Thames Polytechnic, Wellington Street, London SE18.

Recent Progress on Semiconductor Microwave Sources (2 p.m. colloquium) Institution of Electrical Engineers, at Savoy Place, London WC2.

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